Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Repor
E, S	A7501013 Brazil (5 centers), Canada (6 centers), Chile (7 centers), Mexico (2 centers), United States (77 centers)	A multicenter, double-blind, flexible-dose, 6-month trial comparing the efficacy and safety of asnapine with Oanzapine in stable subjects with predominant, persistent negative symptoms of schizophrenia	placebo Route: SL tablet or film-coated tablet asenapine Route: SL tablet Dose Regimen: 5 – 10 mg BID Oanzapine Route: film-coated tablet Dose Regimen: 5 – 20 mg QD	444 planned schizophrenic patients	Not available	26 weeks	Started: December 2004 Status: Ongoing interim
E, S	A7501014 Canada (4 centers), Chile (4 centers), Mexico (1 center), United States (69 centers)	A multicenter, double-blind, flexible-dose, 6-month extension trial comparing the safety and efficacy of asenapine with Oanzapine in subjects who completed protocol A7501013	placebo Route: SL or film-coated tablet asenapine Route: SL tablet Dose Regimen: 5 – 10 mg BID Oanzapine Route: film-coated tablet Dose Regimen: 5 – 20 mg QD	300 Planned schizophrenic patients	Not available	52 weeks total duration	Started: July 2005 Status: Ongoing interim

Type of Trial	Protocol No. (Country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Health Subjects or Diagnosis of Patients	Demographics by Treatment Group (No. of Subjects)	Duration of Treatment	Trial Stat Type o Repor
S, PK	A7501021 United States (39 centers)	A Randomized, Parallel Group, Multiple Dose, 6-Week Study to Evaluate Safety, Tolerability and Pharmacokinetics of asenapine in Elderly Subjects with Psychosis	asenapine Route: SL tablet Dose Regimen: 5 -10 mg BID	120 planned Elderly patients with psychosis disorder	Not available	6 weeks	Started: February 2 Status: Ongoing interim

APPENDIX 3 22-117 Asenapine Literature

[RLL Synopsis of articles that the sponsor has provided]

Backman 2006
Rofecoxib is a potent inhibitor of CYP1A2. CYP1A2 substrates include: clozapine, olanzapine, tacrine, zolmitriptan, and melatonin.

Benzer 2005
Neuroleptic malignant syndrome review. NMS is characterized by fever, muscular rigidity, altered mental status, and autonomic dysfunction. All typical and atypical antipsychotic medications can precipitate the syndrome. NMS has also been associated

with other types of drugs that block central dopamine pathways. All medications implicated in NMS have dopamine D2-receptor antagonist properties. The development of the syndrome is thought to be secondary to decreased dopamine activity in the CNS, either from blockade of D2 receptors or decreased availability of dopamine itself. NMS has features similar to malignant hyperthermia and serotonin syndrome.

The incidence of mortality in cases of NMS is approximately 5-12%. Death usually results from respiratory failure, cardiovascular collapse, myoglobinuric renal failure, arrhythmia, disseminated intravascular coagulation (DIC). Morbidity from NMS includes rhabdomyolysis, pneumonia, renal failure, seizure, arrhythmia, DIC, and respiratory failure.

During treatment with antipsychotic drugs, NMS is more likely to occur soon after initiation of treatment or after an increase in the dose. On average, NMS occurs about 4-14 days after initiation of therapy. Approximately 90% of patients who develop NMS do so within 10 days of beginning antipsychotic treatment.

Chopra 1999
The Neuroleptic Malignant Syndrome: An Indian Experience. The authors discuss 13 cases of NMS treated in an intensive care unit in a large teaching hospital. Mortality rate in these cases was 38%. Patients with NMS had a higher incidence of coexisting medical and neurological illness and a higher mean antipsychotic dose than matched patients treated with antipsychotic medications. Higher potency antipsychotic drugs were also implicated.

Christensen 2002
Fluvoxamine inhibits CYP1A2 and CYP2C19

Craig 2006
'Rhabdomyolysis'
Pathophysiology: rhabdomyolysis is the breakdown of muscle fibers with leakage of potentially toxic cellular contents into the systemic circulation. The final common pathway of rhabdomyolysis may be a disturbance in myocyte calcium homeostasis. Clinical sequelae of rhabdomyolysis include the following:

- Hypovolemia (sequestration of plasma water within injured myocytes)
- Hyperkalemia (release of cellular potassium into the systemic circulation)
- Metabolic acidosis (release of cellular phosphate and sulfate)
- Acute renal failure (nephrotoxic effects of liberated myocyte components)
- Disseminated intravascular coagulation (DIC)

In the U.S., rhabdomyolysis accounts for an estimated 8-15% of cases of acute renal failure. The overall mortality rate for patients with rhabdomyolysis is approximately 5%; however, the mortality rate of any single patient is dependent upon the underlying etiology and any existing comorbidities. Usually presents with muscle pain, and sometimes dark urine. Common risk factors include alcohol abuse, soft tissue

compression, and seizure. Other causative factors include trauma, exertion, drug abuse, metabolic abnormalities, hypothermia, viral illness, flulike illness, burns, sepsis, ischemia, polymyostis, hereditary disorders, drug overdose, and gangrene.

Deng 1990
NMS in Chinese inpatients exposed to neuroleptics.

Friedman 1988
Neuroleptic Malignant Syndrome: The results of a 6-month prospective study of Incidence in a state psychiatric hospital. Just one single case out of 495 patients exposed to antipsychotic medication.

Gelenberg 1988
A Prospective Survey of Neuroleptic Malignant Syndrome in a Short-Term Psychiatric Hospital. Only one patient developed NMS out of 1,470 patients treated with antipsychotic medication (rate of 0.07% per year). The low rate may be due to use of relatively low doses of neuroleptic medication.

Gelenberg 1989- people with history of NMS and rechallenge.

Granfors 2004: ciprofloxacin inhibits CYP1A2

Granfors 2005a: fluvoxamine inhibits CYP1A2

Granfors 2005b: oral contraceptives containing ethinyl estradiol and gestodene inhibits CYP1A2 (markedly increases tizanidine concentrations)

Hermesh 1992
Risk for NMS. Two series of consecutive psychiatric inpatients. At higher risk: patients with Bipolar Disorder and patients treated with injections (higher potency).
Bipolar risk may be at least partly related to lithium exposure and high level of agitation.

Kapur 2001
Dopamine D2 receptor antagonism and their role in the activity of atypical antipsychotic drugs

Keck 1987
Frequency and Presentation of NMS (a prospective study)

Keck 1989
Ditto.

Keck 1991
Declining Frequency of NMS: increased awareness, diagnosis, intervention, treatment, less use of intramuscular medications.

Khan 2001
Placebo treatment and symptom reduction and suicide risk in FDA databases of clinical trials in acute Schizophrenia. Suicide and suicide attempts did not differ significantly. In the placebo group, there was almost no improvement of symptoms.

Mackay 1998
Drug Safety Research Unit, United Kingdom. The DSRU is the centre for prescription event monitoring (PEM). PEM studies are noninterventional observational cohort studies that monitor the safety of newly marketed drugs.

Marder 1997
The effect of risperidone on the five dimensions of Schizophrenia derived by factor analysis: combined results of the North American Trials. Positive symptoms, negative symptoms, disorganized thinking, uncontrolled hostility and excitement, and anxiety/depression. Dr. Marder and colleagues state that risperidone has important over haloperidol. Risperidone produced greater improvements on all five dimensions of Schizophrenia. Especially negative symptoms, uncontrolled hostility and excitement, and anxiety/depression.

Meltzer 1996
Marked elevations of creatine kinase activity associated with antipsychotic drug treatment: markedly elevated serum CK occurred in about 10% of patients treated with the six antipsychotic drugs. May be related to increased permeability of cell membrane. This may be related to serotonergic activity. The increases were not related to NMS. Only one of these patients had rhabdomyolysis as evidenced by myoglobinuria.

Nolte 1991
Rhabdomyolysis associated with cocaine use. Skeletal muscle necrosis without vasulitis.

Roth 1988
Acute rhabdomyolysis associated with cocaine intoxication. Rhabdomyolysis, renal failure, severe liver dysfunction, disseminated intravascular coagulation.

Siris 2001
Suicide and Schizophrenia. Studies estimate that approximately 10% of schizophrenic patients complete suicide. Risk factors include being young, male, early in the course of illness, high socioeconomic background, high intelligence, having high expectations, recently discharged from the hospital, depressive symptoms, and AKATHISIA.
Dr. Siris knows.

Teraro 1999
CPK can be benign

Tohen 1999
Olanzapine treats acute mania

Tohen 2000
Olanzapine treats acute mania

Venkatakrishnan 2005
CYP2D6 inhibited by paroxetine

Muscal 2007
Rhabdomyolysis.
Myalgia, muscle weakness, and dark urine. The triad is rarely observed together. Life-threatening renal failure and disseminated intravascular coagulation are the most dreaded complications. Correct fluid and electrolyte abnormalities.

22-117 BIOPHARM meeting topics

Formulation:

Asenapine tablets are available in two strengths (5 mg and 10 mg). It is intended for sublingual administration. Tablets are manufactured by suspending asenapine maleate into an aqueous solution of gelatin and mannitol, followed by (b) (4) the suspension. Dosing: for Schizophrenia, begin with 5 mg to 10 mg BID, starting with 5 mg BID. For acute mania, begin with 10 mg BID.

Asenapine was initially developed as an oral formulation, but, due to extremely low bioavailability (< 2%), the oral formulation was discontinued in favor of a fast-dissolving tablet for sublingual administration. The low bioavailability of orally administered asenapine is due to extensive first-pass metabolism in the liver (and probably the gut as well). Therefore, a sublingual formulation was developed to circumvent the hepato-gastrointestinal first-pass metabolism. The bioavailability of asenapine after sublingual dosing is considerably higher (35%) than after oral dosing.

Potential problems with formulation and route of administration:
(sublingual is necessary, due to the extremely low bioavailability of asenapine. There is significant loss of a dose if it is swallowed.

Metabolite assessment (per Ron: “commendable”); the assessment was detailed and thorough.

- Parent drug is the active moiety
- Many metabolites ~38; exposures to each are quite low; none are highly prevalent
- None are > 7% of urine radioactivity
- CYP1A2 has some role; fluvoxamine inhibition ↑exposure ~30%
- CYP1A2 induction by carbamazepine ↓ exposure by ~18%
- The smoking induction didn’t really do much, because the subjects were smokers.
- With severe hepatic impairment, AUC increases 7-fold
- With supratherapeutic doses, subjects had acute dystonia
- Tablet administration results in asenapine dissolution of 4 mg/mL

- Sublingual administration yields a mean (across studies) bioavailability of ~36%
- Sublingual bioavailability may be significantly variable, depending on the amount of saliva, swallowing, anticholinergic status, food and water intake
- Look at the three-way administration study: sublingual, supralingual, buccal

APPENDIX 4 INVESTIGATORS AND CLINICAL SITES

----------Appendix for 041004----------

Investigators and Sites

01- George Ainslie, M.D., Department of Veterans Affairs Medical Center, Coatesville, PA
02- Ronald Brenner, M.D., Neurobehavioral Research, Inc. Lawrence, NY
03- George Chappell, M.D., Providence St. Peter Hospital, Olympia, WA
04- Paul Keck, M.D., Univ. of Cincinnati College of Medicine, Cinc., OH
05- Carlos Figueroa, M.D., BHC Alhambra Hospital, Rosemead, CA
07- Clifford Goldman, M.D., ClinCearch, Kenilworth, NJ
08- Robert Horne, M.D., North Las Vegas, NV
09- Adel Wassef, M.D., UT Health Sciences Center, Houston Texas
11- Michael Lesem, M.D., Claghorn-Lesem Clinical Research, Bellaire, TX
12- Robert Litman, M.D., Center for Behavioral Health, Rockville, MD
13- Rick Mofsen, D.O., Clinical Research Associates, St. Louis, MO
14- Steve Potkin, M.D., Univ. of California Irvine Medical Center, Orange, CA
15- Clifford Roberson, M.D., Tennessee Christian Medical Center, Madison, TN
16- David Sack, M.D., Institute for Psychopharmacology Research, Cerritos, CA
17- Scott Segal, M.D., North Miami, FL
18- Seeth Vivek, M.D., Jamaica Hospital Medical Center, Jamaica, NY
19- Tram Tran-Johnson, M.D., California Neuropsychopharmacology Clinical Research Institute, San Diego, CA
20- Cherian Verghese, M.D., Albert Einstein Medical Center, Philadelphia, PA
24- Robert Litman, M.D., Washington Hospital Center, Washington, DC
25- Mohammed Bari, M.D., Synergy Clinical Research, Chula Vista, CA
27-David Brown, M.D., Community Clinical Research, Austin, TX

Site #	Site Name	Randomized (n)	Treated (n)	ITT analysis (n)	Per Protocol analysis (n)
01	Coatesville, PA	3	3	2	0
02	Lawrence, NY	6	6	6	5
03	Olympia, WA	2	2	2	2
04	Cincinnati, OH	3	3	3	2
05	Rosemead, CA	9	9	9	5
07	Kenilworth, NJ	4	3	3	0
08	North Las Vegas, NV	1	1	1	0
09	Houston, TX	9	9	9	5
11	Houston, TX	21	21	21	17
12	Rockville, MD	6	6	6	5
13	St. Louis, MO	14	14	13	13
14	Orange, CA	9	9	8	6
15	Madison, TN	9	9	9	6

16	Cerritos, CA	18	17	16	13
17	North Miami, FL	12	12	12	10
18	Jamaica, NY	9	9	9	8
19	San Diego, CA	20	20	20	18
20	Philadelphia, PA	6	6	6	4
24	Washington, DC	6	6	6	1
25	Chula Vista, CA	9	9	7	5
27	Austin, TX	6	6	6	5
All	Total	182	180	174	130

Combining sites for the ITT analysis:

Twenty sites were planned for the trial. Three sites failed to recruit subjects, and three additional sites were used. A total of 21 sites recruited subjects. To determine potential treatment by site interactions, a minimum of 6 ITT population subjects were required from each center. However, not all centers had 6 ITT subjects. Therefore, for the purposes of analysis, sites 01, 03, 04, 07, and 08 were combined into a composite center with 11 subjects in the ITT population.

Investigators and Sites for Study 041021

01- Scott Aaronson- Sheppard Pratt Health System, Baltimore, MD
02- Jose Alvarez* (did not enroll subjects)
03- Jeffrey Borenstein- Holliswood Hospital, Holliswood , NY
04- Ronald Brenner- Neurobehavioral Research Inc., Floor, Lawrence, NY
05- Toni Carman- Research Strategies Inc., Chagrin Falls, OH
06- Leslie Citrome- Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY
07- Robert Horne- Montevista Hospital, Las Vegas, NV
08- James Knutson- Eastside Therapeutic Resource, Kirkland WA
09- Angelos Halaris- VA Medical Center, Hines IL
10- Robert Litman- Centers for Behavioral Health LLC, Baltimore MD
11- Adam Lowy- Comprehensive NeuroScience Inc., Washington, DC
12- Andrew Cutler- Florida Clinical Research Center LLC, Bradenton FL
13- Denis Mee-Lee- Hawaii Clinical Research Center, Honolulu HI
14- Robert Dahmes- Louisiana Research Associates, New Orleans LA
15- Bradley Diner- Arkansas Psychiatric Clinic PA
16- William Fuller- Avera Research Institute, Sioux Falls SD
17- Clifford Roberson*(did not enroll subjects)
18- Lev Gertsik- California Clinical Trials, Glendale CA
19- Morteza Marandi- Comprehensive Neuroscience Inc., Cerritos CA
20- Steven Holroyd- Research Strategies Inc., Reno NV
21- Mary Knesevich- University Hills Clinical Research, Irving TX
22- Jelena Kunovac- Excell Research, Oceanside CA
23- David Walling- CNS Network, Garden Grove CA
24- Henry Nasrallah- University of Cincinnati Medical Center, Cincinnati OH
25- Stephen Mohaupt- California Clinical Trials, Anaheim CA
26- Rajaprabhakaran Rajarethinam*(did not enroll subjects)
27- Suhas Shanbhag- ClinSearch Inc, Kenilworth NJ
28- Kenneth Sokolski- Clinical Innovations, Santa Ana, CA
29- Nicholas Vatakis- Social Psychiatry Research Institute, New York, NY
30- Alexander Miller- University of Texas Health Science Center at San Antonio
31- Larry Ereshefsky- California Clinical Trials, Culver City CA
32- David Feifel – University of California at San Diego Medical Center
33- Michael Levy*(did not enroll subjects)
34- Duong Nguyen- Woodland International Research Group LLC, Little Rock AR

35- Douglas Dolnak- California Clinical Trials, San Diego CA
36- Leonid Bardenstein- City Psychiatric Hospital #15, Moscow Russia
37- Galina Panteleyeva- Mental Health Research Centre of RAMS, Moscow Russia
38- Margarita Morozova- City Psychiatric Hospital #14, Moscow Russia
39- Anatoly Smulevich- City Psychiatric Hospital #1, Moscow Russia
40- Isaak Gurovich- Moscow Scientific Research Institute of Psychiatry, Moscow Russia
41- Iryna Y. Vlokh- Lviv State Medical University, Lviv Ukraine
42- Oleg S. Chaban- Ukrainian Research Institute of Social, Forensic Psychiatry and Drug Abuse, Kiev Ukraine
43- Vladyslav A. Demchenko- Kiev City Psychoneurological Hospital #2, Kiev Ukraine
44- Valeriy S. Bitensky- Odessa Medical University, Department of Psychiatry, Odessa Ukraine
45- Vitaliy Y. Pishel- Ukrainian Research Institute of Social, Forensic Psychiatry and Drug Abuse, Kiev Ukraine
46- Svitlana Y. Kazakova- Lugansk State Medical University, Department of Psychiatry, Lugansk Regional Psychoneurological Hospital, Lugansk Ukraine
47- Svitlana M. Moroz- Psychosomatic Center of Dnepropetrovsk, Dnepropetrovsk Ukraine
48- Viktor P. Samokhvalov- Crimean State Medical University Department of Psychiatry, Psychotherapy, Narcology, Simferopol Ukraine
49- Lyudmyla N. Yur'yeva- Dnepropetrovsk State Medial Academy, Curanive-preventive Amalgation Interoblast Clinical Psychjneurological Center, Dnepropetrovsk Ukraine

Investigators and Clinical Sites for Study 041022

Title of the clinical trial

A multicenter, randomized, double-blind, flexible -dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using olanzapine positive control in subjects with an acute exacerbation of schizophrenia

Investigators

1) Mohammed Bari
2) Tram Trans-Johnson
3) Steven Potkin
4) Robert Manning
5) Douglas Dolnak
6) Michael Plopper
7) David Marks
8) Madeleine Valencerina
9) Edward Burdick
10) Sohail Punjwani
11) Mark Lerman
12) Ricky Mofsen
13) Joseph McEvoy
14) Steven Glass
15) Jose Canive
16) Miranda Chakos
17) Rakesh Ranjan
18) Mark Novitsky
19) Michael Lesem
20) David Brown
21) Jason Baron
22) Rajinder Shiwach
23) Charles Bailey
24) Mikhail Burdukovsky
25) Nikolay Neznanov
26) Svitlana Kazakova
27) Svitlana Moroz
28) Viktor Samokhvalov
29) Lyudmyla Yur´yeva
30) Oleksandr Napryeyenko
31) Evgenia Reprova [a]
32) Seeth Vivek [a]
33) Philip Janicak [a]

Thirty (30) sites randomized subjects.

[a] Sites did not randomize subjects.

Clinical trial centers

1) Synergy Clinical Research, 5577 University Avenue, Chula Vista, CA 92105
2) CNRI - San Diego LLC, 9466 Black Mountain Road, Suite 100, San Diego, CA 92126
3) UCI Medical Center, 101 The City Drive Way, Orange, CA 92868
4) CNRI – Los Angeles LLC, 8309 Telegraph Road, Pico Rivera, CA 90660
5) California Clinical Trials, 3625 Ruffin Road, Suite 100, San Diego, CA 92123
6) Sharp Mesa Vista Hospital, 7850 Vista Hill Ave., San Diego, CA 92123
7) Optimum Health Services, 7200 Parkway Drive, Suite 116, La Mesa, CA 91942
8) Kedren Community Mental Health Center, 4211 South Avalon Boulevard, Los Angeles, CA 90011
9) Segal Institute for Clinical Research, 1065 N.E. 125th Street, Suite 417, North Miami, FL 33161
10) Segal Institute for Clinical Research, 1065 N.E. 125th Street, Suite 417, North Miami, FL 33161
11) Comprehensive NeuroScience Inc., 1721 Moon Lake Blvd., Suite 109, Hoffman Estates, IL 60194
12) Clinical Research, Inc., 2639 Miami Street, St Louis, MO 63118
13) John Umstead Hospital, 1003 12th Street, Bldg. 32 Ward 321, Butner, NC 27509
14) CNS Research Institute (CRI), 130 White Horse Pike, Clementon, NJ 08021
15) VA Medical Center, 1501 San Pedro SE, Psychiatry Service 116A, Albuquerque, NM 87108
16) SUNY Downstate Medical Center, 450 Clarkson Avenue, Box 1203, Brooklyn, NY 11238
17) Rakesh Ranjan M.D. and Associates Inc., 600 East Smith Road, Suite H, Medina, OH 44256
18) Quantum Clinical Services, 111 North 49th Street, Kirkbride Center, Philadelphia, PA 19139
19) Claghorn-Lesem Research Clinic, Inc., 6750 West Loop South, Suite 1050, Bellaire, TX 77401
20) Community Clinical Research, Inc., 12151 Hunters Chase, Austin, TX 78729
21) MedLabs Research of Houston Inc., 6260 Westpark, Suite 250, Houston, Tx 77057
22) InSite Clinical Research, 2000 Old Hickory Trial, DeSoto, TX 75115
23) Accurate Clinical Trials, 206 Park Place Blvd, Suite 247, Kissimmee, FL 34741
24) City Psyciatric Hospital No4, 75, Obvodny Canal Embankment, 191119, St. Petersburg, Russia

25) City Psyciatric Hospital No6, 13, Obvodny Canal, 193167, St. Petersburg, Russia
26) Lugansk State Medical University, Department of Psychiatry, Lugansk Regional Psychoneurological Hospital, 22, 50 let Oborony Luganska str., Lugansk, 91045 Ukraine
27) Psychosomatic Center of Dnepropetrovsk regional clinic, 14, Oktyabrskaya sq., Dnepropetrovsk, 49616 Ukraine
28) Crimean State Medical University, Department of Psychiatry, Psychotherapy, Narcology Crimean Republican Clinical Psychoneurological Hospital No1, 27, R. Luxemburg str., Simferopol, 95006, Ukraine
29) Dnepropetrovsk State Medical Academy, Curanive-preventiveAmalgation Interoblast Clinical Psychjneurological Center, MoH Ukraine, Dep. Of Psychiatry of Post Graduate Education, 1, Behtereva str., Dnepropetrovsk, 9115, Ukraine
30) National Medical University, Department of Psychiatry, City Clinical Psychonevrological Hospital No1, 103 Frunze Str., Kiev, Ukraine
31) City Psyciatric Hospital No3 named after Skvortsov-Stepanov, 36, Fermskoe shosse, 197341, St. Petersburg, Russia
32) Jamaica Hospital Medical Center, 8900 Van Wyck Expressway, Jamaica, NY 11418
33) Rush University Medical Center, 1720 West Polk, Office 111, Chicago, Il 60612

Investigators and Clinical Sites for Study 041023

Title of the clinical trial

A multicenter, randomized, double-blind, fixed-dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using haloperidol positive control in subjects with an acute exacerbation of schizophrenia (041023)

Investigators

1) Gary Booker
2) Daniel Anderson
3) Saroj Brar
4) David Flaherty
5) Joseph Kwentus
6) Carlos Figueroa
7) Herbert Meltzer
8) Donald Garcia
9) Robert Reisenberg [a]
10) Anantha Shekhar
11) Richard Jaffe
12) Franco Sicuro
13) Bart Sloan
14) Cherian Verghese [b]
15) Daniel Zimbroff
16) Guy Brannon
17) Norman Costigan
18) Alan Jacobson [a]
19) Mohammed Alam [a]
20) Scott Segal
21) Himasiri De Silva
22) Ramanath Gopalan
23) T. P. Sudhakar
24) J. K. Trivedi [a]
25) Ramanathan Sathianathan
26) Sanjay Phadke
27) N. N. Raju
28) Rajesh Nagpal
29) P. S. V. N. Sharma
30) Lakshman Dutt
31) Mikhail Sheifer
32) Alexander Mouzitchenko
33) Alexander Reznik
34) Elena Grigorieva
35) Yuri Alexandrovsky
36) Alexander Kociubynski
37) Mikhail Popov
38) Lala Kasimova
39) Kausar Yakhin
40) Mikhail Burdukovsky [b]
41) Evgenia Rebrova
42) Nikolay Neznanov
43) Victoria Burtea
44) Irina Dan
45) Dan Prelipceanu
46) Petru Boisteanu
47) Monica Ienciu
48) Daniel Vasile
49) Gheorghe Oros

Forty-three (43) sites randomized subjects.
[a] Site was shipped drug but did not screen or randomize any subjects. [b] Site did not randomize any subjects.

Clinical trial centers

1) 851 Olive Street, Shreveport, LA 71104 USA
2) AVI Clinical Research, 3250 Lomita Blvd, Suite 107, Torrance, CA 90505 USA
3) Deaconess Medical Arts Building, 4255 Pearl Road, Suite 105, Cleveland, OH 44109 USA
4) Segal Institute for Clinical Research, 1065 N.E. 125th Street, Suite 417, North Miami, FL 33161 USA
5) Precise Clinical Research, 3531 Lakeland Drive, Brentwood Plaza Suite 1060, Flowood, MS 39232 USA
6) Research Strategies, Inc., 180 N. San Gabriel Blvd., Suite 201, Pasadena, CA 91107 USA
7) Psychiatric Hospital at Vanderbilt, Frank Luton Center, 1601 23rd Avenue South, Suite 306, Nashville, TN 37212 USA
8) Future Search Trials, 4200 Marathon Bldv., Suite 200, Austin, TX 76756 USA
9) Atlanta Center for Medical Research, 811 Juniper Street NE, Atlanta, GA 30308 USA
10) Indiana University, Larue D. Carter Memorial Hospital, 2601 Cold Spring Road, Indinanapolis, IN 46222 USA
11) Belmont Center for Comprehensive Treatment, 4200 Monument Road, Philadelphia, PA 19131 USA
12) Millennium Psychiatric Associates, 12303 De Paul Dr., St. Louis, MO 63044 USA
13) Research Center for Clinical Studies, 17 Old Kings Highway South, Suite 1-2, Darien, CT 06820 USA
14) Keystone Clinical Studies, LLC, 1401 Dekalb Street, Suite 201, Norristown, PA 19401 USA
15) Pacific Clinical Research Medical Group, 1317 W. Foothill Boulevard, Suite 200, Upland, CA 91786 USA
16) Brentwood Research Institute, 1002 Highland Avenue, Suite 400, Shreveport, LA 71101 USA
17) Red Deer Mental Health Clinic, 4733-49 Street, Red Deer, AB T4N 1T6 CANADA
18) Allied Clinical Trials, Inc, 9480 S.W. 77 Avenue, Miami, FL 33156 USA

19) American Medical Research, Inc, 1200 Harger Road, Suite 415, Oak Brook, Il 60523 USA
20) Segal Institute for Clinical Research, Professional Clinical Research, Inc., 1065 N.E. 125th Street, Suite 417, North Miami, FL 33161 USA
21) Clinical Innovations, 801 N. Tustin Ave., Suite 600, Santa Ana, CA 92705 USA
22) Comprehensive Neuroscience, 1010 N. Glebe Rd., Suite 400, Arlington, VA 22201 USA
23) S.V. Medical College, Department of Psychiatry, Tirupati, TAMILNADU 517507 INDIA
24) King George Medical University and G. M. & Associated Hospital, Department of Psychiatry, Shahmina Road, Lucknow, UTTAR PRAD 226003 INDIA
25) Madras Medical College & Government General Hospital, Department of Psychiatry, E.V.R Periyar Salai, Chennai, TAMILNADU 600003 INDIA
26) Hirabai Cowasji Jehangir Medical Research Hospital, Department of Psychiatry, 32 Sassoon Road, Pune, MAHARA 411001 INDIA
27) Government Hospital for Mental Care, Department of Psychiatry, China Waltair, Visakhapatnam, ANDH PRAD 530017 INDIA
28) Manobal Klinik, Department of Psychiatry, A 2 Rajouri Garden, New Delhi, DELHI 110027 INDIA
29) Kasturba Hospital, Department of Psychiatry, P. O. Box No. 7, Manipal, KARNA 576104 INDIA
30) Sheth Vadilal Sarabhai Municipal Hospital, Department of Psychiatry, Ellis Bridge, Ahmedabad, GUJARAT 380006 INDIA
31) Samara Psychiatric Hospital, 78 Nagornaya str., Samara 443 016 RUSSIA
32) City Psychiatric Hospital 14, Psychiatry, 15 Bekhtereva str., Moscow 193019 RUSSIA
33) Moscow Region Psychiatric Hospital #5, Psychiatry, Abramtzevskoe shosse, 1a, Hotkovo, Sergiev-Posad district 142601 RUSSIA
34) Yaroslavl State Medical Academy, Psychiatry Department, Regional Clinical Psychiatric Hospital, Zagorodniy sad, 6, Yaroslavl 150003 RUSSIA
35) City Psychiatric Hospital N12, Psychiatry, 47, Volokolamskoye Shosse, Moscow 123367 RUSSIA
36) Bekhterev Psychoneurological Research Institute, Outpatient Psychiatry, 3 Bekhterev Str., St. Petersburg 193019 RUSSIA
37) City Psychiatric Hospital #3 of Skvortsov-Stepanov, Department #7, Fermskoye shosse, 36, St. Petersburg 194214 RUSSIA
38) City Psichiatric Hospital #1, 41, Ulyanova str, Nizhniy Novgorod 603 155 RUSSIA
39) Kazan State Medical University, Psychiatry and narcology, 49, Butlerova str., 80, Volkova str., Kazan 420012 RUSSIA
40) 4th Psychiatric Hospital, Psychiatry, 75, Obvodniy Canal embankment, St. Petersburg 191119 RUSSIA
41) City Psychiatric Hospital #3 of Skvortsov-Stepanov, Department #7, Fermskoye shosse, 36, St. Petersburg 197341 RUSSIA
42) City Psychiatric Hospital #6, Obvodnoy Canal embankment, 13, St. Petersburg 193167 RUSSIA
43) Spitalul de Psihiatrie si Neurologie Brasov, Sectia Clinica de Psihiatrie, Str. Mihai Eminescu nr. 18, Brasov 500079 ROMANIA
44) Spitalul Clinic de Psihiatrie Prof. Dr. Alex. Obregia, Sos. Berceni, Nr.10-12, sector 4, Bucuresti 041914 , ROMANIA
45) Spitalul Clinic de Psihiatrie Prof. Dr. Alex. Obregia, Pavilionul 9, Sos. Berceni, Nr.10-12, sector 4, Bucuresti 041914 ROMANIA
46) Spitalul Universitar de Psihiatrie Socola Iasi, Str. Bucium nr. 36, Iasi 700265 ROMANIA
47) Spitalul Clinic de Psihiatrie E. Pamfil, Str. Iancu Vacarescu nr. 21, Timisoara, 300182 ROMANIA
48) Spitalul Clinic de Urgenta Militar Central Dr. Carol Davila, Clinica de Psihiatrie, Cal. Plevnei nr. 137, Bucuresti 060011 ROMANIA
49) Spitalul Clinic de Psihiatrie si Neurologie, Str. Louis Pasteur nr. 26, Oradea 410154 ROMANIA

Investigators and Clinical Sites for Study A7501004

Investigator(s)

1. Svetlozar Haralanov
2. Rinaldo Shishkov
3. Nagesh Brahmavar Pai
4. Ramanathan Sathianathan
5. Dattatreya Dhavale
6. Nimesh Desai
7. Padma Sudhakar Thatikonda
8. Mariappa Srinivasa
9. Won-Myong Bahk
10. Prof. Hyun-Sang Cho
11. Mohd Daud Dalip and Ahmad Hatim Sulaiman (Previous PI)
12. Kim Kah Lau
13. Suarn Singh Jasmit Singh
14. Rosanna de Guzman
15. Elizabeth E. Rondain
16. Vicente G. Rosales
17. Adrian Ionescu
18. Mihai Gheorghe
19. Anatoly Boleslavovich Smulevich
20. Yuri Anatolyevich Aleksandrovsky
21. Alla Sergeevna Avedisova
22. Margarita A. Morozova
23. Valeriy Bitenskyy
24. Svetlana M. Moroz
25. Volodymyr Abramov
26. Svitlana Kazakova
27. Iryna Spirina
28. Oleksandr K. Napryeyenko
29. Oleksandr O. Filts
30. Mohammed Younus Alam
31. Steven Garth Potkin
32. Guy Emilio Brannon
33. David Warren Brown
34. Glen Michael Dempsey
35. Larry Ereshefsky
36. Jose Edgardo Gamez
37. Steven Jerome Glass
38. James A. Knutson
39. Chandra Shekar Krishnasastry*
40. Mark Norbert Lerman
41. Adam Frederick Lowy
42. David Morris Marks
43. Dr. Jerry George Olsen
44. Michael Gregory Plopper
45. Raj Parsram Rajani
46. Rakesh Ranjan
47. Morteza Marandi and David Andrew Sack (Previous PI)
48. Alan C. Whitters*
49. Rajinder Shiwach
50. Richard Louis Jaffe
51. Ronald Loewy Brenner
52. Michael David Lesem
53. Seeth Vivek
54. Andrew Jon Cutler
55. Suhas R. Shanbhag
56. Joseph Allen Kwentus
57. Charles Richard Conway*
58. Jose J. Alvarez
59. Joseph Patrick McEvoy
60. Robert Enoch Litman
61. Toni L. Carman*
62. Steven Holroyd*
63. Mohammed Abdul Bari
64. Craig Alan Ginsberg*
65. Charles Edward Bailey Jr.
66. Duong Huu Nguyen
67. Eduardo Cifuentes

* Did not randomize subjects

1. University Hospital Sv. Naum, Second Psychiatric Clinic, Sofia, 1113 BULGARIA
2. Varna University Hospital "Sveta Marina", Third Psychiatric Clinic, 1, "Hristo Smirnenski" Varna, 9010 BULGARIA
3. Department of Psychiatry, Justice K.S. Hegde Charitable Hospital, K.S. Hegde Medical Sciences Complex, Deralkatte, Karnataka, Mangalore 574 160 INDIA
4. Madras Medical College and Government General Hospital, Department of Psychiatry, Chennai, Tamil Nadu 600 003 INDIA
5. Poona Hospital and Research Centre, 27 Sadashiv Peth, Pune, 411 030 INDIA
6. Institute of Human Behavior & Allied Sciences, Department of Psychiatry, New Delhi, 110095 INDIA
7. Sri Venkateshwara Medical College, Department of Psychiatry, Tirupati, Andhra Pradesh 517507 INDIA
8. Spandana Nursing Home, No. 549/46, 6th Main, Rajajinagar, 4th Block, Bangalore, Karnataka 560 010 INDIA
9. The Catholic University of Korea, St. Mary's Hospital, 62 Yeouido-dong, Yeongdeungop-gu, Seol KOREA, REPUBLIC OF
10. Severance Mental Health Hospital, Department of Psychiatry, 696-6 Tanbeol-dong, Gwangju-si, Gyeonggi-do 464-100 KOREA, REPUBLIC OF
11. Hospital Mesra Bukit Padan, P.O. Box 11342, Kota Kinabalu, Sabah 88140 MALAYSIA
12. Jabatan Psikiatri, Hospital Pulau Pinang, Jalan Residensi, Pulau Pinang, 10990 MALAYSIA
13. Hospital Bahagia U/U Kinta, Tanjung Rambutan, Perak Darul Ridzuan 31250 MALAYSIA
14. Philippine General Hospital, Department of Psychiatry, Taft Avenue, Manila PHILIPPINES
15. Makati Medical Center, Room 121, First Floor, 2 Amorsolo Street, Legaspi Village, Makati City PHILIPPINES
16. Sto. Tomas University Hospital, Room 1010, Medical Arts Building, A.H. Lacson, Manila PHILIPPINES and University of Santo Tomas Hospital, Department of Neurology and Psychiatry, Esoana Street, Sampaloc, Manila PHILIPPINES
17. Spitalul de Psihiatrie si pentru Masuratori de Siguranta Sapoca, Sectia de Psihiatric Acuti Nifon, Localitatea Magura, Jud. Buzau 127320 ROMANIA
18. Spitalul Militar Central, Clinica de Psihiatrie, Calea Plevnei 137, Bucuresti, Sector 6 060011 ROMANIA
19. Mental Health Research Center, Kashirskoye Shosse, 34, Moscow, 115522 RUSSIAN FEDERATION
20. Clinical Hospital No. 12, Volokolamskoe Shosse 47, Moscow, 123357 RUSSIAN FEDERATION and State Scientific Research Centre named after Serbsky, Kropotkinsky per. 23, Moscow, 119034 RUSSIAN FEDERATION
21. Clinical Hospital No. 12, Volokolamskoe Shosse 47, Moscow, 123357 RUSSIAN FEDERATION and State Scientific Research Centre named after Serbsky, Kropotkinsky per. 23, Moscow, 119034 RUSSIAN FEDERATION
22. Mental Health Research Centre, Kashirskoe Shosse, 34, Moscow, 115522 RUSSIAN FEDERATION and Psychiatric Hospital #14, Ul. Bekhtereva, 15, Moscow, 115477 RUSSIAN FEDERATION
23. Odessa Regional Psychiatric Clinical Hospital, 9, Acad. Vorobyeva Str., Odessa, 65006 UKRAINE
24. Psychosomatic Center of Dnepropetrovsk Regional Clinical Hospital, 14, Zhovtneva Ploshchad, Dnepropetrovsk, 49616 UKRAINE
25. Donetsk Regional Clinical Psychiatric Hospital, 190, Odintsova Street, Donetsk, 83037 UKRAINE
26. Lugansk Regional Clinical Psychoneurological Hospital, 22, 50-let Oborony Luganska Kvartal, Lugansk, 91045 UKRAINE
27. Dnepropetrovsk Regional Psychiatric Centre, 1, Behtereva Str., Dnepropetrovsk, 49115, UKRAINE
28. Kiev City Psychiatric Hospital #1, 103A Frunze Str., Kiev, 04080 UKRAINE
29. Lviv Regional Clinical Psychiatric Hosptial, 95, Kulpakrivska Str., Lviv, 79021 UKRAINE
30. AMR Conventions Research, Unit 9, 4S100 Route 59, Naperville, IL 60563 UNITED STATES and American Medical Research, Inc., Suite 415, 1200 Harger Road, Oak Brook, IL 60523 UNITED STATES and Mercy Provena Hospital, 1325 North Highland, Aurora, IL 60506 UNITED STATES
31. UCI Medical Center, Neuropsychiatric Center, 101 The City Drive South, Orange, CA 92868 UNITED STATES
32. Brentwood, 1006 Highland Avenue, Shreveport, LA 71101 UNITED STATES and Brentwood Research Institute, LLC, Suite 400, 1002 Highland Avenue, Shreveport, LA 71101 UNITED STATES
33. Community Clinical Research Incorporated, 4411 Medical Parkway, Austin, TX 78756 UNITED STATES and Community Clinical Research, Inc., 12151 Hunters Chase, Austin, TX 78729 UNITED STATES
34. Albuquerque Neuroscience, Inc., Suite 203, 715 Dr. Martin Luther King Jr. Avenue Northeast, Albuquerque , NM 87102 UNITED STATES and Albuquerque Regional Medical Center, 601 Dr. Martin Luther King Jr. Avenue Northeast, Albuquerque, NM 87012 UNITED STATES
35. California Clinical Trials Medical Group, 55 Wing, Main Floor, 1509 Wilson Terrace, Glendale, CA 91206 UNITED STATES and Glendale Adventist Medical Center, 1509 Wilson Terrace, Glendale, CA 91206 UNITED STATES
36. Berma Research Group, Suite 515, 7150 West 20th Street, Hialeah, FL 33016 UNITED STATES and Southern Winds Hospital, 4225 West 20th Avenue, Hialeah, FL 33016 UNITED STATES

37. CNS Research Institute, 130 White Horse Pike, Clementon, NJ 08021 UNITED STATES and CNS Research Institute, PC, 218 A Sunset Blvd, Willingboro, NJ 08046 UNITED STATES and CNS Research Institute, PC, Suite 202, 1113 Hospital Drive, Willingboro, NJ 08046 UNITED STATES
38. Eastside Therapeutic Resource, 830 6th Street South, Kirkland, WA 98033 UNITED STATES and Fairfax Hospital, 10200 Northeast 132nd Street, Kirkland, WA 98034 UNITED STATES
39. Clinical Research Services at Tennessee Christian Medical Center, 320 Hospital Drive, Madison, TN 37115 UNITED STATES and Tennessee Christian Medical Center, 500 Hospital Drive, Madison, TN 37115 UNITED STATES
40. Alexian Brothers Behavioral Health Hospital, 1650 Moon Lake Blvd., Hoffman Estates, IL 60194 UNITED STATES and Alexian Center for Psychiatric Research, Suite 200, 1786 Moon Lake Bouelvard, Hoffman Estates IL 60194 UNITED STATES
41. Comprehensive Neuroscience, Inc., Psychiatric Institute of Washington, 4228 Wisconsin Avenue, Northwest, Washington, DC 20016 UNITED STATES
42. Alvarado Parkway Institute, 7050 Parkway Drive, LaMesa, CA 91942 UNITED STATES and Optimum Health Services, Suite 116, 7200 Parkway Drive, La Mesa, CA 91942 UNITED STATES
43. Laurel Ridge Treatment Center, 17720 Corporate Woods Drive, San Antonio, TX 78259-3509 UNITED STATES and University of Texas Health Science Center at San Antonio, Department of Pharmacology, MSC 6220, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900, UNITED STATES
44. Sharp Mesa Vista Hospital, 7850 Vista Hill Avenue, San Diego, CA 92123, UNITED STATES
45. California Clinical Trials, Suite 204, 1000 South Anaheim Boulevard, Anaheim, CA 92805 UNITED STATES and Western Medical Center, 1025 South Anaheim Boulevard, Anaheim, CA 92805 UNITED STATES
46. Marymount Hospital, Trudell Behavioral Health Center, 12300 McCracken Road, Garfield Heights, OH 44125 UNITED STATES and Rakesh Ranjan, MD & Associates, Inc., Suite 150, 801 East Washington Street, Medina, OH 44256 UNITED STATES and Rakesh Ranjan, MD & Associates, Inc., Suite 203, 83 North Miller Road, Akron, OH 44333 UNITED STATES and Rakesh Ranjan, MD & Associates, Inc. Suite 309 & 206, 5010 Mayfield Road, Lyndhurst, OH 44124 UNITED STATES
47. College Hospital Cerritos, 10802 College Place, Cerritos, CA 90703 UNITED STATES and Comprehensive NeuroScience, Inc, 10802 College Place, Cerritos, CA 90703 UNITED STATES
48. Cedar Rapids Psychiatry, 3705 River Ridge Drive Northeast, Cedar Rapids, IA 52402 UNITED STATES and Mercy Medical Center, 701 Tenth Street Southeast, Cedar Rapids, IA 52403 UNITED STATES
49. InSite Clinical Research, The Cedars Hospital, 2000 Old Hickory Trail, DeSoto, TX 75115 UNITED STATES
50. Belmont Center for Comprehensive Treatment, 4200 Monument Road, Philadelphia, PA 19131 UNITED STATES
51. Brunswick Hall at Brunswick Hospital Center, 81 Louden Avenue, Amityville, NY 11701 UNITED STATES and Neurobehavioral Research, Inc., 371 Central Avenue, Lawrence, NY 11559 UNITED STATES
52. Claghorn-Lesem Research Clinic, 1019 Ashland, Houston, TX 77008 UNITED STATES and Claghorn-Lesem Research Clinic, Suite 1050, 6750 West Loop South Bellaire, TX 77401 UNITED STATES
53. Jamaica Hospital Medical Center, 8900 Van Wyck Expressway, Jamaica, NY 11418 UNITED STATES
54. Core Research, Inc., 3914 State Road 64 East, Bradenton, FL 34208, UNITED STATES and Manatee Glens, 2020 26th Avenue East, Bradenton, FL 34208, UNITED STATES
55. ClinSearch, Inc., 1700 Galloping Hill Road, 3rd Floor, Kenilworth, NJ 07033 UNITED STATES and Trinitas Hospital, 655 East Jersey Street, Elizabeth, NJ 07201 UNITED STATES
56. Brentwood Behavioral Healthcare of MS, 3531 Lakeland Drive, Flowood, MS 39232 UNITED STATES and Joseph Kwentus, MD, 801 Steels Pointe, Madison, MS 39110 UNITED STATES and Precise Research Centers Brentwood Plaza Suite 1060, 3531 Lakeland Drive, Flowood, MS 39232 UNITED STATES
57. Saint Louis University, School of Medicine, Department of Psychiatry, 1221 South Grand Boulevard, St. Louis, MO 63104 UNITED STATES
58. Circles of Care, 400 East Sheridan Road, Melbourne, FL 32901 UNITED STATES and Health First Clinical Research Institute, Suite 202, 1355 South Hickory Street, Melbourne, FL 32935 UNITED STATES
59. Duke University Medical Center, Civitan Building, 2213 Elba Street, Durham, NC 27705 UNITED STATES and John Umstead Hospital, Adult Admission Unit, 1003 12th Street, Butner, NC 27509 UNITED STATES
60. CBH Health, LLC, Dominion Hospital, 2960 Sleepy Hollow Road, 3 South Research, Falls Church, VA 22044 UNITED STATES
61. Windsor Hospital, 115 East Summit Street, Chagrin Falls, OH 44022 UNITED STATES
62. West Hills Hospital, 1240 East Ninth Street, Reno, NV 89512 UNITED STATES
63. Synergy Clinical Research Center, 1908 Sweetwater Road, National City, CA 91950 UNITED STATES and Synergy Clinical Research Center, 5550 University Avenue, San Diego, CA 92105 UNITED STATES and University Medical Center, 5550 University Avenue, San Diego, CA 92105 UNITED STATES
64. Brooke Glen Behavioral, Attn: Clinical Trials Office, 7170 Lafayette Avenue, Fort Washington, PA 19034 UNITED STATES
65. Park Place Behavioral Health Care, 206 Park Place Boulevard, Kissimmee, FL 34741 UNITED STATES
66. Woodland International Research Group, LLC, Suite 3, 1014 Autumn Road Little Rock, AR 72211 UNITED STATES
67. Palmetto Lowcountry Behavioral Health, 2777 Speissegger Drive, Charleston, South Carolina 29405 UNITED STATES

Investigators and Clinical Sites for Study A7501005

Investigator(s)

1. Vichra Milanova
2. Gueorgui Popov
3. Jitendra Kumar Trivedi
4. Ganpat Kodarbhai Vankar
5. Rajeshkumar Chandrakant Maniar
6. Ranjive Mahajan
7. Alok Sarin
8. Rajesh Sagar
9. ByungOok Lee and Duk-In Jon (Previous PI)
10. Jae-Min Kim
11. Jun-Soo Kwon
12. Ahmad Hatim Sulaiman and Mohd Daud Dalip (Previous PI)
13. Maria Asela Casem
14. Jacqueline Sy
15. Dan Prelipceanu
16. Radu Mihailescu
17. Isaac Yakovlevich Gurovich
18. Alexander M. Reznik
19. Nikolay G. Neznanov
20. Kausar Yakhin
21. Simavi Vahip
22. Olcay Yazici
23. Viktor Samokhvalov
24. Vladyslav Demchenko
25. Valeriy Pidkorytov and Petro Voloshyn (Previous PI)
26. Oleg Z. Golubkov
27. Jason Dennis Baron
28. Himasiri DeSilva
29. Donald J. Garcia
30. Michael Edward Balkunas and Mahlon Stewart Hale (Previous PI)
31. Valentin Isacescu*
32. J. Gary Booker
33. Raymond Manning
34. Ricky Stuart Mofsen
35. Mary Ann Knesevich
36. Robert J. Reichler
37. Michael J. Rieser
38. Neil Mark Richtand
39. Ronald Murray Salomon
40. Radu V. Saveanu
41. Tram K. Tran-Johnson
42. Cherian Verghese*
43. Richard H. Weisler
44. Ramanath Gopalan
45. Denis Mee-Lee
46. Sohail S. Punjwani
47. Daniel D. Anderson
48. Kashinath Yadalam
49. Willis Holloway
50. Edward Peter Burdick
51. Robert Lynn Horne
52. Pauline Smith Powers
53. Dan Louis Zimbroff
54. Anjali Pathak
55. Scott Daniel Segal
56. David Howard Flaherty
57. Vicki Burdine

* Did not randomize subjects
Fifty-five (55) sites randomized subjects

Clinical trial center(s)

1. University Hospital Aleksandrovska, Pschiatric Clinic, 1 Georgi Sofiiski Str., Sofia, 1404 BULGARIA
2. Varna University Hospital "St. Marina", Second Psychiatric Clinic, 1, "Hristo Smirnenski," Str, Varna, 9010 BULGARIA
3. King George's Medical University, Department of Psychiatry, Lucknow, Uttar Pradesh 226003 INDIA
4. BJ Medical College and Civil Hospital, HOD Psychiatry, Ward E1, Ahmedabad, 380 016 INDIA
5. Sheth Vadilal Sarabhai General Hospital, Department of Psychiatry, Sheth K. M. School of Post Graduate Medicine & Research, Ellisbridge, Ahmedabad 380 006 INDIA
6. Dayanand Medical College and Hospital, Ludhiana, 141001 INDIA
7. Vidyasagar Institute of Mental Health & Neurosciences, No 1 Institutional Area Nehru Nagar, New Delhi, Delhi 110 065 INDIA
8. All India Institute of Medical Sciences, Department of Psychiatry, Ansari Nagar, New Delhi 110 029 INDIA
9. National Health Insurance Corporation Ilsan Hospital, Department of Psychiatry, 1232 Baekseok-dong, Ilsan-gu, Goyang-si, Gyeonggi-do 411-719 KOREA, REPUBLIC OF

10. Chonnam National University Hospital, Department of Psychiatry, 8 Hak-dong, Dong-gu, Kwangju-si, Chonnam 501-757 KOREA, REPUBLIC OF
11. Seoul National University Hospital, Department of Psychiatry, 28 Yongon-dong, Chongno-gu, Seoul, 110-744 KOREA, REPUBLIC OF
12. University Malaya Medical Centre, Department of Psychological Medicine, Faculty of Medical Medicine, University of Malaya, Kuala Lumpur, 50603 MALAYSIA
13. Baguio General Hospital and Medical Center, Department of Psychiatry, Corner of Marcos Highway and Governor Pack Road, Baguio City, 2600 PHILIPPINES
14. Vicente Sotto Memorial Medical Center, B. Rodriguez Street, Cebu City, 6000 PHILIPPINES
15. Spitalul Psihiatrie "Prof. de. A. Obregia", Sectia 9, Sos Berceni 10-12, Bucharest, Sector 4 041914 ROMANIA
16. Spitalul de Psihiatrie, "Prof. de. A. Obregia" sectia 11, Sos Berceni 10-12, Bucuresti, Sector 4 041914 ROMANIA
17. Moscow Research Institute of Psychiatry, Poteshnaya ul., 3, Moscow, 107076 RUSSIAN FEDERATION
18. Moscow Region Psychiatric Hospital N 5, Sergievo-Posadskii raion, Moskovskaya ooblast, Khotkovo, 141371 RUSSIAN FEDERATION
19. St. Petersburg State Medical University, City Psychiatric Hospital No. 6, Dept. of Psychiatry, Nab. Obvodnogo Kanala, 13, St. Petersburg, 193167 RUSSIAN FEDERATION
20. Kazan City Psychoneurological Clinical Hospital, 80 Volkova ul, Kazan, 420012 RUSSIAN FEDERATION
21. Ege University Medical Faculty, Psychiatry Department, Bornova, Izmir, 35100 TURKEY
22. University of Istanbul Istanbul Medical School, Department of Psychiatry, Millet Caddesi, Istanbul/Capa, 34093 TURKEY
23. Crimean State Psychiatric Hospital #1, 27, Rozy Luxemburg Str., Simferopol, Crimea 95006 UKRAINE
24. Kiev City Psychiatric Hospital #2, 8, Miropolska Str., Kiev, 02660 UKRAINE
25. Institute of Neurology, Psychiatry and Narcology of the Academy of Medical Science of Ukraine, 8, Academic Pavlova Str., Kharkiv, 61068 UKRAINE
26. Zaporizhzhia Regional Clinical Psychiatric Hospital, 31, Sedova Str., Zaporizhzhia, 69057 UKRAINE
27. IntraCare Hospital, 7601 Fannin, Houston, TX 77054 UNITED STATES and Medlabs Research of Houston, Inc, Suite 322, 6250 Westpark, Houston, TX 77057 UNITED STATES
28. Clinical Innovations, Suite 600, 801 North Tustin Avenue, Santa Ana, CA 92705 UNITED STATES and St. Joseph Hospital, 1100 West Stewart Drive, Orange, CA 92863-5600 UNITED STATES
29. FutureSearch Trials, Suite 200, 4200 Marathon Boulevard, Austin, TX 78756 UNITED STATES and Texas NeuroRehab Center, Pecos Unit, 1106 West Dittmar, Austin, TX 78756 UNITED STATES
30. New Britain General Hospital, 100 Grand Street, New Britain, CT 06050 UNITED STATES and New Britain General Hospital, Behavioral Health Research, 32 Hawkins Street, New Britain, CT 06050 UNITED STATES
31. Optimum Health Services, Suite F, 3998 Vista Way, Oceanside , CA 92056 UNITED STATES and Tri-City Medical Center, 4002 Vista Way, Oceanside, CA 92056 UNITED STATES
32. Office of J. Gary Booker, MD, Suite 204, 827 Margaret Place, Shreveport, LA 71101 UNITED STATES and Promise Specialty Hospital, 1800 & 1842 Irving Place, Shreveport, LA 71101 UNITED STATES
33. Aurora Charter Oak Behavioral Health Care, 1161 East Covina Boulevard, Covina, CA 91724 UNITED STATES and CNRI - Los Angeles LLC, 8309 Telegraph Road, Pico Rivera, CA 90660 UNITED STATES
34. Clinical Research Inc., St. Alexius-Jefferson Campus, 2639 Miami Street, St. Louis, MO 63118 UNITED STATES
35. Timberlawn Mental Health Hospital, 4600 Samuell Boulevard, Dallas, TX 75228 UNITED STATES and University Hills Clinical Research, Suite 250, 102 Decker Drive, Irving, TX 75062 UNITED STATES
36. Pacific Institute of Mental Health, Suite 510, 2150 North 107th Street, Seattle, WA 98133-9009 UNITED STATES and Stevens Hospital, 21601 76th Avenue West, Edmonds, WA 98026 UNITED STATES
37. Office of Michael J. Rieser MD, Suite 202, 2801 Palumbo Drive, Lexington, KY 40509 UNITED STATES and Ridge Behavioral Health, 3050 Rio Dosa Drive, Lexington, KY 40509 UNITED STATES
38. Cincinnati VA Medical Center, 3200 Vine Street, Cincinnati, OH 45220 UNITED STATES and University Hospital, 234 Goodman Avenue, Cincinnati, OH 45219 UNITED STATES and University of Cincinnati Medical Center, 231 Albert Sabin Way, Cincinnati, OH 45267-0559 UNITED STATES
39. Vanderbilt University School of Medicine, Vanderbilt Adult Psychiatry Clinic, Village at Vanderbilt, Suite 200, 1500 21st Avenue South, Nashville, TN 37212 UNITED STATES and Vanderbilt University School of Medicine, Vanderbilt Psychiatric Hospital, 1601 23rd Avenue South, Nashville, TN 37212 UNITED STATES
40. The Ohio State University Medical Center, Neuropsychiatric Facility, 1670 Upham Drive, Columbus, OH 43210 UNITED STATES
41. Aurora Behavioral Health Care/San Diego, 11878 Avenue of Industry, San Diego, CA 92128 UNITED STATES and CNRI-San Diego, Suite 100, 9466 Black Mountain Road, San Diego, CA 92126 UNITED STATES
42. Central Montgomery Mental Health/Mental Retardation Center, Inc., 1100 Powell Street, Norristown, PA 19401 UNITED STATES and Keystone Clinical Studies, LLC, Suite 201, 1401 Dekalb Street Norristown, PA 19401 UNITED STATES and Montgomery Hospital Medical Center, 1301 Powell Street, Norristown, PA 19401 UNITED STATES
43. Holly Hill Hospital, 3019 Falstaff Road, Raleigh, NC 27610 UNITED STATES and Office of Richard H. Weisler, MD, PA, Suite 125, 700 Spring Forest Road, Raleigh, NC 27609 UNITED STATES
44. Comprehensive Neuroscience of Northern Virginia, Suite 400, 1010 North Glebe Road, Arlington, VA 22201 UNITED STATES and Virginia Hospital Center Arlington, 1701 North George Mason Drive Arlington, VA 22205 UNITED STATES
45. Hawaii Clinical Research Center, 26th Floor and Suite 3704, 1750 Kalakaua Avenue, Honolulu, HI 96826 UNITED STATES and Kahi Mohala, 91-2301 Fort Weaver Road Ewa Beach, HI 96706 UNITED STATES

46. Ft. Lauderdale Hospital, 1601 East Las Olas Boulveard, Ft. Lauderdale, FL 33301 UNITED STATES and Professional Clinical Research Inc c/o Segal Institute for Clinical Research, Suite 417, 1065 Northeast 125th Street, North Miami, FL 33161 UNITED STATES
47. AVI Clinical Research, Suite 104, 105, 107, & 109, 3250 Lomita Blvd, Torrance, CA 90505 UNITED STATES and Del Amo Hospital, 23700 Camino Del Sol, Torrance, CA 90505 UNITED STATES and View Heights Convalescent Hospital, 12619 South Avalon Boulevard, Los Angeles, CA 90061 UNITED STATES
48. Institute for Neuropsychiatry, Suite 150, 2829 Fourth Avenue, Lake Charles, LA 70601 UNITED STATES and Lake Charles Clinical Trials, Suite 340, 2770 Third Avenue. Lake Charles, LA 70601 UNITED STATES and Lake Charles Memorial Hospital, 1701 Oak Park Boulevard, Lake Charles, LA 70601 UNITED STATES and Medical & Occupational Clinic of Lake Charles, Suite 225, 2770 Third Avenue, Lake Charles, LA 70601 UNITED STATES
49. Cutting Edge Research Group, 6613 North Meridian Avenue, Oklahoma City, OK 73116 UNITED STATES and St. Anthony Hospital, 1000 North Lee Street, Oklahoma City, OK 73101 UNITED STATES
50. Behavioral Clinical Research, Suite 417, 1065 Northeast 125th Street, North Miami, FL 33161 UNITED STATES and South Beach Community Hospital and Medical Center, 630 Alton Road, Miami Beach, FL 33139 UNITED STATES
51. Montevista Hospital, 5900 West Rochelle, Las Vegas, NV 89103 UNITED STATES and UNKNOWN, Suite 4, 2915 West Charleston, Las Vegas, NV 89102 UNITED STATES
52. Fairwinds Treatment Center, 1569 South Fort Harrison, Clearwater, FL 33756, UNITED STATES and University of South Florida, Department of Psychiatry and Behavioral Medicine, 3515 East Fletcher Avenue, Tampa, FL 33613 UNITED STATES
53. Pacific Clinical Research Medical Group, Suite 200, 1317 West Foothill Boulevard, Upland, CA 91786 UNITED STATES and Riverside Center for Behavioral Medicine, 5900 Brockton Avenue, Riverside, CA 92506 UNITED STATES
54. A.P. Psychiatric and Counseling Services, 5251 Emerson Street, Jacksonville, FL 32207 UNITED STATES and Ten Broeck Hospital, 6300 Beach Boulevard, Jacksonville, FL 32216 UNITED STATES
55. Hollywood Pavilion, 1201 North 37th Avenue, Hollywood, FL 33021 UNITED STATES and Memorial Regional Hospital, 3501 Johnson Street, Hollywood, FL 33021 UNITED STATES
56. Atlantic Shores Hospital, 4545 North Federal Highway, Ft. Lauderdale, FL 33308 UNITED STATES and Fidelity Clinical Research, Inc. c/o Segal Institute for Clinical Research, Suite 417, 1065 Northeast 125th Street, North Miami, FL 33161 UNITED STATES
57. Valle Vista Health System, 898 East Main Street, Greenwood, IN 46143 UNITED STATES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Levin
5/1/2008 07:00:12 AM
MEDICAL OFFICER

Gwen Zornberg
5/1/2008 07:16:30 PM
MEDICAL OFFICER
CMC review was completed 11 APR 2008 recommending AE. Dr. Levin reported to me today verbally that no major toxicities including cases of aplastic anemia evident in clinical data. The data supporting acute efficacy in SZ and BP appear satisfactory.

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: April 23, 2008

From: Suchitra Balakrishnan, M.D., Ph.D.

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Keith Kiedrow
Regulatory Project Manager
Division of Psychiatry Products

Subject: QT-IRT Consult to NDA 22,117

This memo responds to queries from DPP regarding arrhythmia related issues associated with Asenapine (specifically cases of sinus pause seen with healthy volunteers). The QT-IRT received and reviewed the following materials:

- The Summary of Clinical Safety provided on 8/30/07
- Electronic datasets for the PR and QRS intervals provided by the Sponsor with Study Report A7501001
- QT- IRT review for Study INT 00036960

Background

The QT- IRT recently reviewed Study INT 00036960. In this randomized, placebo-controlled, double-blind, multicenter, parallel-group trial, subjects with schizophrenia or schizoaffective disorder received asenapine 5/10 mg b.i.d., asenapine 15/20 mg b.i.d., placebo, or quetiapine 375 mg b.i.d. for 16 days. Asenapine failed to exclude a 10-ms increase in the QT interval at both doses. With 35 subjects per arm, a dose-response relationship was not observed for asenapine. The review division has requested review of additional information with respect to pro-arrhythmic potential of asenapine, specifically cases of sinus pauses seen in the healthy volunteer studies

1 Previous Clinical Experience

There are 63 trials in the asenapine schizophrenia and bipolar mania clinical development programs that were conducted with the sublingual formulation of asenapine as of the database cut-off of 15 January 2007. The safety information from the completed Phase 2/3 trials was

analyzed in five cohorts.

Table 11 Number of Subjects Treated in the Asenapine Schizophrenia and Bipolar Mania Clinical Programs (continued)

Subject Group	Total Number of Subjects	Number of Subjects 5 or 10 mg BID
Combined Phase 2/3 for Bipolar Mania and Schizophrenia		
asenapine	2251	1953
placebo	706	
comparator	1134	
Ongoing Phase 2/3 Clinical Trials		
asenapine	~ 1045	~1045
placebo	~611	
comparator	~405	

1.1 Deaths:
As of the January 15, 2007 database cutoff date, there were 11 deaths in all asenapine groups, 1 death in the placebo group, and 3 deaths in the olanzapine group. One patient is reported to have died due to cardiac failure in ongoing trials.
Reviewers Comment: There are no deaths in the Clinical Summary reported as sudden cardiac death or due to significant ventricular arrhythmia. One patient died due to aspiration during a seizure 3 months after discontinuing study drug.

1.2 Arrhythmias
In cohort E (combined Phase 2/3 for Bipolar Mania and Schizophrenia), the incidence of tachycardia (17), sinus tachycardia (5) sinus bradycardia (13), ventricular extrasystoles (2) were higher than in the placebo group but comparable to olanzapine.
There was 1 case of atrial fibrillation in the placebo group. There were 2 cases of "cardiac flutter" and 1 case of WPW syndrome with asenapine. The proportion of patients who experienced heart blocks was similar in the asenapine (BBB-1, LBBB-2, and RBBB-3) and olanzapine groups.

Reviewers Comment
The most common arrhythmias seen in all studies were tachycardia and bradycardia and occurred in the subjects dosed between 5-10 mg b.i.d. Narratives for the patients with cardiac flutter and WPW syndrome were not available for review. However, the number of cases of atrial fibrillation/flutter was similar in active and placebo groups in all cohorts.

1.3 Sinus arrests
In cohort F (Clinical pharmacology studies in healthy volunteers) there were 9 episodes of sinus arrest reported in the subjects who received asenapine < 5mg and 4 reports of nodal rhythm. The sponsor attributes these events to neurally mediated reflex bradycardia (NMRB). The sponsor provided the following report in the ISS.

> "Neurally Mediated Reflex Bradycardia (NMRB) is a benign, self-limiting event, and the most common cause of vasovagal syncope. It involves central hypovolemia,

vasodepression, and a degree of bradycardia; the bradycardia may be accompanied by periods of asystole that are due to either sinus pause or heart block. NMRB can occur with or without sinus pause and is typically associated with postural challenge. Healthy, young volunteers with a high resting vagal tone display a higher incidence of NMRB than do psychiatric patients.

"Cardiovascular studies in anesthetized cats, anesthetized dogs, and conscious rabbits indicate that the main hemodynamic effects of intravenous asenapine are a decrease in arterial blood pressure, probably as a result of α1-adrenergic blocking activity, and orthostatic hypotension. The results of these in vivo studies also show that asenapine displays marked anti-histaminergic properties while no effects on cholinergic or ß-adrenergic systems are observed.

"There were no cases of NMRB reported in subjects with schizophrenia or bipolar disease. Four healthy volunteers receiving asenapine and one volunteer receiving placebo had reports of NMRB with sinus pause. These cases are briefly described.

- A 27 year old Caucasian male, and a former competing pentathlon athlete (resting supine heart rate of 52 bpm and blood pressure of 104/60 mm/Hg, standing heart rate of 70 bpm with a blood pressure of 112/82 mm/Hg), received 0.7 mg asenapine intravenously over 30 minutes in study 25506. Forty-five minutes after the start of the infusion, the subject sat up in bed for a blood pressure measurement and complained of dizziness and feeling unwell. He fell back in the bed and the ECG monitor showed asystole of > 8 seconds (recording stopped after 8 seconds). The bed was tilted head down at only a slight angle that allowed the investigator to intervene with brief chest compressions. During this intervention, the subject experienced 3 consecutive episodes of sinus pause of > 8 seconds duration each (recording stopped after 8 seconds). Severe bradycardia with intermittent nodal complexes and AV dissociation persisted until the investigator administered two intravenous injections of 0.6 mg atropine. Normal sinus rhythm was then restored and further recovery was uneventful. The peak asenapine plasma level in this volunteer was 1850 pg/ml. The investigator and a consulting cardiologist concluded this event was causally related to drug administration.
- A 22 year old Caucasian male, endurance athlete (resting heart of 58 bpm), received a 30-mg oral dose of asenapine in study 25501. Approximately 2.5 hours after the dose and 5 minutes after breakfast, the subject sat up in bed and felt dizzy and nauseated. The ECG telemetry strip showed heart rate slowing and an 8.7-second pause. This was followed by heart block with nodal bradycardia, which spontaneously converted to sinus rhythm. He had another episode 2 hours later. Both episodes resolved spontaneously without intervention while the subject remained in the supine position.
- A 33 year old Caucasian male received sublingual asenapine 0.15 mg in study 25511. Approximately 2.5 hours after the dose, he experienced NMRB with syncope 7 minutes after standing which resolved spontaneously without intervention when the subject was in the supine position. The subject's heart rate slowed from 100 bpm to 43 bpm within 19 seconds followed by syncope with an

associated 6.2-second sinus pause.
•A 24 year old Caucasian male received sublingual placebo in study 25511 at baseline and experienced dizziness followed by a 6.4-second sinus pause after 4 minutes of standing. The subject's heart rate slowed from 110 bpm to 40 bpm. The event resolved spontaneously without intervention. The subject continued in the study to received asenapine without any subsequent problem.
•A 52 year old Caucasian male in study 041033 received asenapine 5 mg and fluvoxamine 25 mg BID after having received fluvoxamine for the past 4 days. One hour after his combined dose, he developed sinus pauses. The sinus pauses occurred during 10 minutes while the volunteer was sleeping and lasted for 3 to 12 seconds. The subject recovered the same day and continued in the trial. This event was considered to be due to NMRB.

"In summary, NMRB occurred in four healthy volunteers receiving asenapine and one healthy volunteer receiving placebo. In the asenapine clinical program, NMRB with sinus pause was observed mainly in young and athletic healthy volunteers with high vagal tone and occurred after a postural change following asenapine or placebo. This was not seen in psychiatric patients."

Reviewers Comment: Since these events occurred only in healthy volunteers, the explanation provided by the sponsor appears reasonable.
In conscious dogs, orally administered asenapine induced dose-dependent negative inotropic and positive chronotropic effects accompanied by ECG changes (QTc interval prolongation), orthostatic hypotension on tilt with marked tachycardia. The results of a study in isolated canine Purkinje fibers indicate that asenapine induced mainly decreases in action potential duration, in particular on APD50. These effects were associated with a decrease in the plateau of the action potential reflecting mainly block of calcium channel current. Decreases in action potential duration were dose-dependent and were more pronounced under low stimulation rate (0.33Hz) than under normal stimulation rates (1Hz). N-desmethylasenapine induced comparable effects (decreased action potential duration, particularly APD50, but at approximately 10 times higher concentrations. It is possible that the sinus pauses observed in healthy volunteers could be due to negative inotropic effects of the drug secondary to inhibition of sodium or calcium current. However, NMRB secondary to α-receptor blockade appears to be a more plausible explanation.

1.4 Effects on PR and QRS intervals-Study INT 00036960
The QT-IRT also analyzed the PR and QRS datasets provided by the sponsor for Study INT 00036960. The change from baseline compared to placebo (ΔPR and ΔQRS) and corrected for placebo (ΔΔPR and ΔΔQRS with 2 sided 90% CI) was computed. Compared to placebo both drugs (asenapine and quetiapine) exerted similar effects on the PR and QRS intervals. Slight shortening of both intervals was observed (maximum change ~-9 ms and -3 ms respectively). There is no clinical significance to these findings.

1.5 Other Cardiac AEs
Asenapine may induce orthostatic hypotension associated with dizziness (postural), tachycardia and, in some patients syncope, especially early in treatment, probably reflecting its α1-adrenergic antagonistic properties. It appears that healthy volunteers are more susceptible to the blood

pressure lowering effect of asenapine. In Phase 2/3 studies, the incidence of orthostatic related adverse events was similar in the asenapine group compared to the other comparators. The incidence of syncope was low, 0.5% in the asenapine 5-10 mg BID dose group, which was comparable to the olanzapine group (0.4%) and slightly greater than placebo (0.1%).

QT-IRT COMMENTS:
It appears that the arrhythmia related AEs associated with asenapine are similar to those of olanzapine and consistent with class effects based on our review of the summary of clinical safety, non-clinical summary and additional analysis of ECG intervals in Study INT 0036960

Thank you for requesting our input into the development of this product under NDA 22117. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Suchitra Balakrishnan
4/23/2008 02:00:08 PM
MEDICAL OFFICER

Norman Stockbridge
4/23/2008 06:06:06 PM
MEDICAL OFFICER

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	22117
Brand Name	Sycrest®
Generic Name	Asenapine (ORG 5222)
Sponsor	Organon USA Inc.
Indication	Treatment of schizophrenia and acute manic or mixed episodes associated with Bipolar I disorder
Dosage Form	Fast dissolving sublingual tablets
Drug Class	Psychotropic agent
Therapeutic Dose	5 to 10 mg b.i.d.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	20 mg b.i.d.
Application Submission Date	30 August 2007
Review Classification	Standard NDA
Date Consult Received	3 Oct 2007
Clinical Division	DPP / HFD 130
PDUFA Date	30 June 2008

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

This is a positive study by the ICH E14 guideline: the upper 95% confidence interval exceeded 10 ms for all doses.

In this randomized, placebo-controlled, double-blind, multicenter, parallel-group trial, subjects with schizophrenia or schizoaffective disorder received asenapine 5/10 mg b.i.d., asenapine 15/20 mg b.i.d., placebo, or quetiapine 375 mg b.i.d. for 16 days. A dose-response relationship was not observed for asenapine as shown in the following table. We note that with the small sample size (less than 35 subjects pre arm), the study was not powered to detect a dose-response relationship using the primary endpoint.

FDA Analysis: The Point Estimates and 90% CI Corresponding to the Largest Upper Bounds for Asenapine by Dose Group

Treatment	Time, h	Mean ΔΔQTcF, ms	90% CI, ms
Asenapine 5 mg b.i.d., N=30	3	5.0	-1.5, 11.4
Asenapine 10 mg b.i.d., N=27	2	10.5	4.5, 16.5
Asenapine 15 mg b.i.d., N=33	3	8.7	3.0, 14.4
Asenapine 20 mg b.i.d., N=29	4	4.9	-1.9, 11.6

Cross reference: reviewer's analysis in Table 10

An exposure-response analysis conducted by both the sponsor and FDA reviewers showed that asenapine prolonged the QTcF interval in a concentration-dependent manner (described in section 5.2.1.2). The model predicted mean ΔΔQTcF at a mean C_{max} of 10.6 ng/mL, which corresponds to an asenapine dose of 20 mg b.i.d., is 6 ms (8 ms, 90% upper confidence limit). Asenapine 20 mg b.i.d., the maximum tolerated dose in patients with schizophrenia, provides a 2-fold increase in exposure over the highest clinical dose (10 mg b.i.d.) and adequately covers the plasma concentrations observed in phase 2b/3 clinical studies (Figure 1). We note, however, that subjects with severe hepatic impairment have 7-fold increase unbound AUC. The magnitude of QT prolongation in these subjects is not known.

Because asenapine belongs to a pharmacological class of compounds associated with QT/QTc prolongation, the sponsor used quetiapine 375 mg b.i.d. as the positive control. The magnitude of quetiapine effects on the QTc interval is not well characterized. In this study, the difference from placebo in LS mean time-matched QTcF change from baseline at T_{max} was 7 ms (90% CI: 1, 13) on Day 10 and 10 (90% CI: 3, 17) ms on Day 16. The exposure-response relationship for quetiapine was similar to the observed relationship in Study R076477-SCH-1014 in NDA 21,999 (Table 13). Therefore, assay sensitivity with quetiapine could be established.

2 PROPOSED LABEL

The following is our recommendations for labeling. We defer all final labeling decisions to the review division.

5.9 QT Prolongation

The effects of Sycrest® on the QT interval were evaluated in a dedicated QT study [*see CLINICAL STUDIES* (14.3)]. Sycrest® causes a mild ~~(<5 ms)~~ increase in the corrected QT (QTc) interval ~~but the magnitude of the effect is such that it is not expected to be clinically relevant~~. Electrocardiogram (ECG) measurements were taken at various time points during the Sycrest® clinical trial program testing therapeutic doses (5-10 mg b.i.d.) and any post-baseline QT prolongations exceeding 500 ms were reported in comparable rates to placebo in the short-term trials.

Sycrest® should be used cautiously in combination with drugs that are known to prolong the QTc interval including Class 1A (e.g., quinidine, procainamide) or Class 3 (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other

class of medications known to prolong the QTc interval. Sycrest® should also be used cautiously in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

14.3 Thorough QT/QTc Trial

A trial assessing the potential QT/QTc prolonging effect of Sycrest® 5 mg, 10 mg, 15 mg, and 20 mg b.i.d. and placebo was conducted in 151 clinically stable patients with schizophrenia. Electrocardiographic assessments were performed throughout the dosing interval both at baseline and steady state. ~~The mean increase in QTc from baseline at C_{max}, as derived from exposure-response analysis, was 1.9 ms, 3.0 ms, 3.7 ms, and 4.9 ms for Sycrest® 5 mg, 10 mg, 15 mg, and 20 mg b.i.d., respectively; and 7.5 ms for quetiapine 375 mg b.i.d..~~ There was a concentration-dependent increase in QTc interval. ~~Categorical analyses for this study revealed that~~ No patients treated with Sycrest® experienced QTc increases >60 ms from baseline measurements, nor did any patient experience a QTc of >500 ms. Additionally, there were no reports of Torsade de Pointes or any other adverse events associated with delayed ventricular repolarization.

3 BACKGROUND

Asenapine (also referred to as Org 5222) is a psychotropic (psychopharmacologic) agent with a unique receptor binding profile that is available for sublingual administration. Asenapine's pharmacological profile displays potent multi-receptor antagonism for a combination of serotonin, dopamine, noradrenaline, and histamine receptors and no appreciable activity at muscarinic cholinergic receptors. The sponsor believes the compound may be effective in the treatment of various symptom domains in schizophrenia and/or mood disorders, and that it may have low propensity for the induction of extrapyramidal symptoms (EPS).

3.1 MARKET APPROVAL STATUS

Asenapine is not approved for marketing in the USA or elsewhere.

3.2 PRECLINICAL INFORMATION

Source: nonclinical summary

ORG 5222, tested at 0.1, 0.3, and 1 µM concentrations using HEK-293 cells transfected with HERG produced statistically significant and concentration-dependent decreases in hERG current amplitude (30.9 ± 4.3%, 51.2 ± 5.7%, and 69.8 ± 5.8%, respectively) when compared to vehicle control. The IC50 for ORG 5222, the concentration computed from the concentration-response relationship at which 50% of total current was suppressed, was 0.3 µM.

The results of a study in isolated canine Purkinje fibers indicate that asenapine induced mainly decreases in action potential duration, in particular on APD_{50}. These effects were associated with a decrease in the plateau of action potential involving mainly calcium channel current. Decreases in action potential duration were dose-dependent and were more pronounced under low stimulation rate (0.33Hz) than under normal stimulation rates (1Hz). N-desmethylasenapine induced comparable effects (decreased action potential duration, particularly APD_{50}) but at approximately 10 times higher concentrations.

Oral ORG 5222 (1-50 mg/kg) administered to conscious dogs induced dose-dependent negative inotropic and positive chronotropic effects, accompanied by shortening of the PR interval, less marked hypotensive effects and dose-dependently prolonged QTc. The QRS interval was shortened but only at the higher dose. Moderate orthostatic hypotension was observed on tilt which was accompanied by marked and dose-dependent tachycardia. Behavioral excitation was observed at dose levels from 2.5 mg/kg onwards. Sublingual administration of ORG 5222 (0.01-1 mg/kg) induced dose-dependent tachycardia in the absence of negative inotropy and hypotension. QTc was only markedly prolonged by the highest dose used which also lengthened QRS. A similar moderate orthostatic hypotension was seen upon tilt but the accompanying tachycardia was considerably less than after oral administration. Sublingually given Org 5222 caused minor and transient behavioral excitation at the highest dose only, but induced long lasting tranquilization especially at the mid and high doses.

Reviewer's Comment: Non clinical data are suggestive of dose-and concentration-dependent QT prolongation.

3.3 PREVIOUS CLINICAL EXPERIENCE

Source: Clinical Summary

There are 63 trials in the asenapine schizophrenia and bipolar mania clinical development programs that were conducted with the sublingual formulation of asenapine as of the database cut-off of 15 January 2007. The safety information from the completed Phase 2/3 trials was analyzed in five cohorts. As of the January 15, 2007 database cutoff date, there were 11 deaths in the all asenapine group, 1 death in the placebo group, and 3 deaths in the olanzapine group.

One subject in the long-term schizophrenia trial (study 25517) died from aspiration during a *seizure*. The subject, a 33 year old Caucasian female had received asenapine 5-10 mg for one month during the study and was discontinued due to a *seizure*. Three months later, she had another seizure that resulted in death. This death is not included in the tables and listings because it occurred more than 30 days after the last dose.

The most common adverse event leading to death was suicide (6 asenapine 5-10 mg b.i.d. [0.3%], 2 olanzapine [0.2%]). In addition, there were 2 drug overdoses that led to death, 1 in the asenapine 5-10 mg b.i.d. group (accidental overdose) and 1 in the olanzapine group (overdose) neither of the overdose cases was due to asenapine overdose. One subject died of cardiac failure in an ongoing trial

The most common cardiac AEs were bradycardia (3.6%) and tachycardia (2.8%)

A 27 year old male Caucasian healthy volunteer (study 25506), collapsed 15 minutes after the end of a 30 minute intravenous infusion of asenapine (0.7 mg). Just prior to collapse, the subject reported feeling dizzy and unwell and then fell back on the bed. The event was reported as *asystole*; however, this event was considered to be due to neurally mediated reflex bradycardia. The subject recovered.

A 22 year old Caucasian male (resting heart of 58 bpm), received a 30 mg oral dose of asenapine in study 25501. Approximately 2.5 hours after the dose, the subject sat up in bed and felt dizzy and nauseated. The ECG telemetry strip showed heart rate slowing and an *8.7 second pause*. *This was followed by heart block with nodal bradycardia*, which spontaneously converted to sinus rhythm. He had another episode 2 hours later. Both episodes resolved spontaneously without intervention while the subject remained in the supine position.

Vomiting, *syncope*, hypotension were experienced by a 23 year old female (study 25504), following asenapine (4 mg dose) on Day 13, which led to discontinuation from the study (considered related to study drug). Subject recovered the same day.

Grand mal *convulsion* occurred in a 59 year old male (study 25505), following asenapine (2 mg dose) on Day 6, which led to discontinuation from the study. Subject recovered the same day. According to the investigator, the grand mal convulsion was due to hyponatraemia (sodium: 114 mmol/L) secondary to polydipsia and was not related to study drug (see Section 2.7.4.2.1.5.7 on hyponatraemia).

In the long-term schizophrenia study 25517, ECGs were performed at Screening, Weeks 3, 6, 24, and endpoint, and the tracings were read by a central laboratory. Analyses included interval changes from baseline (descriptive statistics), categorical changes, outlier analysis, and post-baseline markedly abnormal changes in morphology. The most frequently reported ECG related AE in the asenapine group (1.2%) was Electrocardiogram QT corrected interval prolonged (0.6% in the olanzapine treatment group).

Reviewers Comment: QT prolongation was also noted in clinical studies. Seizures can be expected in this population due to lowering of seizure threshold due to drug, polydipsia/substance abuse. However, syncope/asystole and an 8.7 sinus pause were noted in young healthy subjects.

3.4 CLINICAL PHARMACOLOGY

Appendix 7.1 summarizes the key features of asenapine's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the following:

- Clinical study report for Study A750-1001 and associated electronic data sets
- Report for Study INT00036960 and associated electronic data sets
- Digital ECGs in the ECG Warehouse for Study A750-1001

4.2 TQT STUDY

4.2.1 Protocol Number and Title

Protocol A7501001: A Double-Blind, Parallel, Multicenter Study to Assess the Effect of Asenapine, Quetiapine (Seroquel®), and Placebo on the QTc Interval in Patients With Schizophrenia

4.2.2 Study Dates

Clinical Trial Start: 29 June 2004
Clinical Trial Completion: 20 December 2004

4.2.3 Objectives

The objectives of this trial were to estimate the effect of asenapine, compared with placebo, on the QTc interval; to estimate the differences between asenapine and

quetiapine on the QTc interval; and to characterize the pharmacodynamic response of asenapine with respect to dose and plasma concentration.

4.2.4 Study Description

4.2.4.1 Design

This was a randomized, placebo-controlled, double-blind, multicenter, parallel-group trial with 2 treatment periods.

Following screening and medication tapering if needed, each subject was evaluated for a minimum of 24 days, consisting of a 5-day single-blind placebo run-in phase, a 16-day treatment phase that included 2 treatment periods, and a post-treatment restabilization period.

4.2.4.2 Controls

The Sponsor used both placebo and active (quetiapine) controls.

4.2.4.3 Blinding

Study drug was administered in a double-blind, double-dummy fashion during periods 1 and 2.

4.2.5 Treatment Regimen

4.2.5.1 Treatment Arms

Subjects were assigned to 1 of 4 treatment groups as shown in Table 1.

Table 1: Treatment Groups

Group	Drug	Period 1: Target Dose (w/Titration)	Period 2: Target Dose (w/Titration)
1	Asenapine	5 mg BID × 10 days	10 mg BID × 6 days
2	Asenapine	15 mg BID × 10 days	20 mg BID × 6 days
3	Quetiapine	375 mg BID × 10 days	375 mg BID × 6 days
4	Placebo	BID × 10 days	BID × 6 days

Sponsor's Table 2, page 26 of CSR for A750-1001

Table 2: Dose Schedule Showing Titration

Day	Placebo	Asenapine		Quetiapine
		5/10 BID	15/20 BID	
1	Placebo BID	5 mg BID	5 mg BID	25 mg BID
2	Placebo BID	5 mg BID	10 mg BID	50 mg BID
3	Placebo BID	5 mg BID	15 mg BID	100 mg BID
4	Placebo BID	5 mg BID	15 mg BID	150 mg BID
5	Placebo BID	5 mg BID	15 mg BID	200 mg BID
6	Placebo BID	5 mg BID	15 mg BID	250 mg BID
7	Placebo BID	5 mg BID	15 mg BID	300 mg BID
8	Placebo BID	5 mg BID	15 mg BID	375 mg BID
9	Placebo BID	5 mg BID	15 mg BID	375 mg BID
10	Placebo BID	5 mg BID	15 mg BID	375 mg BID
11	Placebo BID	10 mg BID	20 mg BID	375 mg BID
12	Placebo BID	10 mg BID	20 mg BID	375 mg BID
13	Placebo BID	10 mg BID	20 mg BID	375 mg BID
14	Placebo BID	10 mg BID	20 mg BID	375 mg BID
15	Placebo BID	10 mg BID	20 mg BID	375 mg BID
16	Placebo BID	10 mg BID	20 mg BID	375 mg BID

Sponsor's Table 5, page 34 of CSR for A750-1001

4.2.5.2 Sponsor's Justification for Doses

The asenapine dose range in the present trial included the lowest effective dose (5 mg b.i.d.) and the maximally tolerated dose (20 mg b.i.d.). This was to allow determination of the dose-response and the construction of a pharmacokinetic/pharmacodynamic model of the QTc effect.

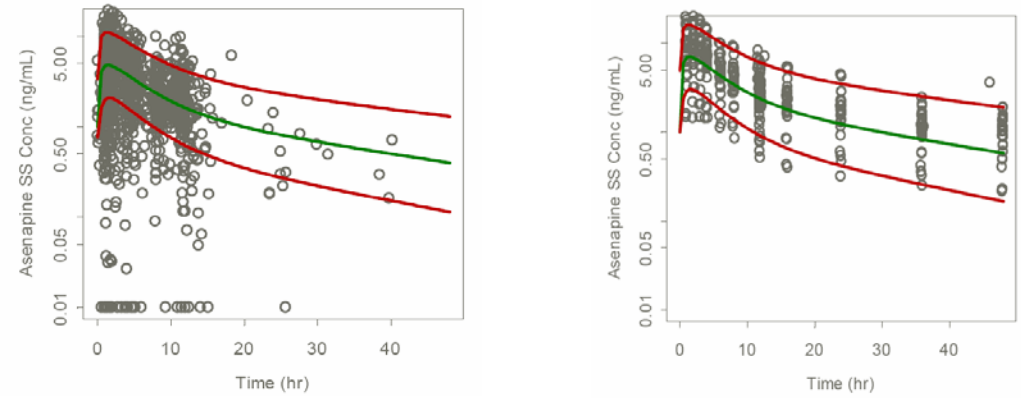
Quetiapine was included to assure assay sensitivity and to make direct comparisons with asenapine. The mean change from baseline in QTc for quetiapine without metabolic inhibition was 4.8 and 5.7 ms for Fridericia's and the population-based correction, respectively. The dose of 750 mg per day approximates the maximally recommended dose, and was the same as in the trial described above.

Reviewer's Comments:

- *Asenapine dose selection for the QT study was reasonable. The exposures achieved with 20mg b.i.d. asenapine reasonably cover the exposures after 10 mg b.i.d. in the phase IIb/III trial in schizophrenia indication (*Figure 1*).*
- *From a dose perspective, administration of quetiapine 375 mg b.i.d. is acceptable as an active control. According to the label, efficacy in schizophrenia was demonstrated in a dose range of 150 to 750 mg/day however, QTc prolongation is not well characterized.*
- *Although quetiapine dose (375mg b.i.d.) was slightly lower than the dose used in another QT study (400 mg b.i.d., NDA 21,999), the exposures achieved are fairly similar.*

- *In subjects with severe hepatic impairment, a 7-fold increase in exposure was observed. The effect on the QT interval with this increase in exposure is not known.*

Figure 1: Asenapine concentrations from phase IIb/III study (Schizophrenia indication; 10mg b.i.d. SS) and QT study (20mg b.i.d. SS)



Source: Sponsor's population PK report (population-pk-phase-2-3-asenapine.pdf) Figures 1 and 3)

4.2.5.3 Instructions with Regard to Meals

Subjects were to have had their meals before dosing and to be finished eating at least 15 minutes before each dose; they were allowed to drink water up to 5 minutes prior to the dose. The timing of meals and medication administration was to be consistent throughout the trial for each subject.

4.2.5.4 ECG and PK Assessments

Serial ECG recordings (triplicates) and corresponding pharmacokinetic (PK) samples were obtained on Days 1, 10, and 16: prior to and 1, 2, 3, 4, 6, 8, and 12 hours following the morning dose of study medication. The ECGs were recorded immediately before the blood draws and the 12-hour postdose ECGs were performed prior to the evening dose of study medication. On Day 16, additional PK samples were obtained at 16, 24, 36, and 48 hours following the morning dose.

4.2.5.5 Baseline

The baselines were defined as the ECGs recorded on the last day of the 5-day single blind placebo run-in phase. Time-matched baselines were used in the primary analysis.

4.2.6 ECG Collection

Digital ECGs (GE Medical MAC 1200 with onscreen display) were performed in triplicate (other than at Screening and Closeout) at the time points specified during the placebo run-in and treatment phases. Subjects were to be supine for at least 10 minutes prior to the 12-lead ECG assessments and a 2-minute period was required between recordings. Study site personnel were instructed to minimize subject stress and anxiety throughout the trial, particularly during the ECG recordings and to minimize environmental sympathetic and autonomic intervention during the ECG recordings.

Electronic data files were sent to a central lab for manual interpretation.

Measured ECGs were interpreted and intervals verified and re-measured onscreen by a cardiologist. All ECGs for a particular subject were overread by the same cardiologist.

All interval measurements were made from a single lead: lead II, or lead I if lead II was not possible, or lead V4 if lead I and lead II were not possible. A complete interpretation was performed. Interval measurements were performed in a digital environment using electronic calipers. Each interval was measured as a single measurement of an averaged complex from the chosen lead, utilizing a validated median template methodology, with a sample of at least 3-5 original complexes.

Machine-interpreted data (PR, QRS, QT, QTc, ventricular rate (VR)) from screening and closeout ECGs was recorded on the 12-lead ECG CRFs.

Reviewers comment: It is unclear if the ECG readers were blinded to time and treatment identifiers.

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

This trial was designed to evaluate 120 subjects with schizophrenia on Day 10: 30 subjects in each of 4 treatment groups. A total of 151 subjects were enrolled, of whom 148 (114 men, 34 women) took at least 1 dose of study drug (the safety analysis set). Inclusion criteria included normal baseline ECG, age between 18-65 yrs of age and BMI between 17-36 kg/m^2.

The safety analysis set yielded 125 subjects who completed at least 10 days of treatment--the treatment groups at Day 10 ranged in size from 30 to 33 subjects. Thirty-four subjects, 23% of the safety analysis set, discontinued double-blind treatment. The most frequent reason for subject discontinuation was withdrawal of consent (23 subjects, 16%). Eight subjects (5%) withdrew due to adverse events; 7 of these withdrawals were prior to Day 10 and included a withdrawal due to a serious adverse event that began as a PTSS. Subjects in the active treatment groups withdrew consent more often than subjects in the placebo group.

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

The primary endpoint was time-matched change from baseline in QTcF on Day 10 and Day 16 after dosing. Time-matched QTcF was calculated for each subject by subtracting the QTcF at each nominal time on the baseline day from the QTcF at the same nominal time on Day 10 and Day 16. The Sponsor used a repeated measurement Analysis of Variance (ANOVA) to compare asenapine and quetiapine with placebo and used a one-way ANOVA to compare asenapine with quetiapine. The repeated measurement ANOVA for the asenapine with placebo comparisons consisted of treatment, subject within treatment, time, and time by treatment effects.

For all dose combinations of asenapine (5/10 mg b.i.d., 15/20 mg b.i.d.), the largest upper limits of the two-sided 90% Confidence Interval for asenapine vs. placebo differences

after baseline adjustments were above the 10 ms threshold. Analysis of the primary endpoint demonstrated that asenapine had a positive effect on the QTc interval in this trial.

Table 3: Difference in Least Square Means of Asenapine from Placebo of Time Matched Change from Baseline in QTcF (Manually Read)

Treatment Comparison	Time Post-Dose (hour)	N	Difference	90% Lower	90% Upper
Day 10					
Asenapine 5 mg b.i.d. vs Placebo	1	30	0.9	-5.0	6.9
	2	30	2.6	-3.3	8.6
	3	30	5.0	-1.0	**10.9**
	4	30	5.8	-0.2	**11.7**
	6	30	4.1	-1.9	**10.0**
	8	29	5.9	-0.1	**11.9**
	12	29	0.9	-5.1	6.8
Asenapine 15 mg b.i.d. vs Placebo	1	33	5.6	-0.2	**11.4**
	2	33	6.4	0.6	**12.3**
	3	33	8.7	2.9	**14.5**
	4	33	8.0	2.2	**13.8**
	6	33	5.1	-0.8	**10.9**
	8	33	6.1	0.3	**12.0**
	12	32	1.0	-4.8	6.9
Day 16					
Asenapine 10 mg b.i.d. vs Placebo	1	27	3.4	-3.1	**10.0**
	2	27	10.5	3.9	**17.1**
	3	27	-0.4	-6.9	6.2
	4	27	9.3	2.7	**15.9**
	6	26	6.2	-0.4	**12.8**
	8	26	5.2	-1.4	**11.9**
	12	26	0.4	-6.2	7.1
Asenapine 20 mg b.i.d. vs Placebo	1	29	2.6	-3.8	9.1
	2	29	5.2	-1.2	**11.7**
	3	29	-1.1	-7.5	5.4
	4	28	5.1	-1.4	**11.6**
	6	29	-1.3	-7.8	5.1
	8	29	-1.8	-8.2	4.7
	12	29	-1.4	-7.9	5.0

Sponsor's Section 11.1.2.01.01.01, pages236-239 of CSR for A750-1001

Reviewer's Comment: The sponsor used quetiapine as a positive control for the QT study. The following table presented the difference in least square means of quetiapine from placebo of time matched changed from baseline in QTcF.

Table 4: Difference in Least Square Means of Quetiapine from Placebo of Time Matched Change from Baseline in QTcF (Manually Read)

Treatment Comparison	Time Post-Dose (hour)	N	Difference	90% Lower	90% Upper
Day 10					
Quetiapine 375 mg b.i.d. vs Placebo	1	30	2.5	-3.5	8.4
	2	30	6.7	0.8	12.7
	3	30	7.5	1.5	13.4
	4	30	7.9	1.9	13.8
	6	30	2.7	-3.2	8.7
	8	30	10.9	4.9	16.8
	12	30	3.1	-2.8	9.0
Day 16					
Quetiapine 375 mg b.i.d. vs Placebo	1	27	4.1	-2.5	10.7
	2	27	9.9	3.3	16.5
	3	27	6.9	0.4	13.5
	4	27	6.8	0.3	13.4
	6	27	3.1	-3.4	9.7
	8	27	4.9	-1.7	11.5
	12	27	-0.6	-7.2	6.0

Sponsor's Section 11.1.2.01.01.01, pages236-239 of CSR for A750-1001

4.2.7.2.2 Categorical Analysis

A summary of the number of absolute QTcF outliers by day and time is presented in Table 5.

Table 5: Categorization of QTcF Data by Gender and Treatment Group

		Number (Percent) of Subjects by Maximum Post-dose QTcF (msec)								
		---------- Males ----------				---------- Females ----------				
		<430	430-<450	450-<500	≥500		<450	450-<470	470-<500	≥500
Treatment	N	n(%)	n(%)	n(%)	n(%)	N	n(%)	n(%)	n(%)	n(%)
Baseline										
Placebo	28	27 (96.4)	1 (3.6)	0 (0.0)	0 (0.0)	7	7 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 5 mg	33	33 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 15 mg	26	26 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	12	12 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Quetiapine 375 mg	27	27 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	10	10 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Day 1[a] through Day 10										
Placebo	28	27 (96.4)	0 (0.0)	1 (3.6)	0 (0.0)	7	6 (85.7)	0 (0.0)	1 (14.3)	0 (0.0)
Asenapine 5 mg	33	29 (87.9)	4 (12.1)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 15 mg	26	24 (92.3)	1 (3.8)	1 (3.8)	0 (0.0)	12	9 (75.0)	2 (16.7)	1 (8.3)	0 (0.0)
Quetiapine 375 mg	27	26 (96.3)	1 (3.7)	0 (0.0)	0 (0.0)	10	9 (90.0)	1 (10.0)	0 (0.0)	0 (0.0)
Day 11 through Day 16										
Placebo	27	26 (96.3)	1 (3.7)	0 (0.0)	0 (0.0)	5	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 10 mg	24	21 (87.5)	3 (12.5)	0 (0.0)	0 (0.0)	4	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asenapine 20 mg	20	20 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	10	8 (80.0)	1 (10.0)	1 (10.0)	0 (0.0)
Quetiapine 375 mg	22	22 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	7	6 (85.7)	1 (14.3)	0 (0.0)	0 (0.0)

Source: 11.1.2.01.01.05
[a] Post dose

Sponsor's Table 36, page 93 of CSR for A750-1001

For the 5 subjects who had QTcF values ≥450 ms (for men) or ≥470 ms (for women), increases from baseline in time matched QTcF ranged from 14 ms to 61 ms. According to the Sponsor, two of these subjects experienced adverse events from the cardiac-disorders system organ class during the trial: Subject 10010016 (hypertension) and Subject 10050009 (increased blood pressure).

During Period 1 (Days 1 through 10), the number of subjects who experienced increases in QTcF ≥30 ms ranged from 7 of 38 subjects (18.4%) in the placebo group to 15 of 37 subjects (40.5%) in the quetiapine group. Three subjects had QTcF increases ≥60 ms. Similarly, the number of subjects who experienced QTcF increases ≥30 ms during Period 2 (Days 11 through 16) ranged from 5 of 32 subjects (15.6%) who received placebo to 9 of 29 subjects (31%) in the quetiapine group; 2 placebo-treated subjects had QTcF increases ≥60 ms. No asenapine treated subject had a QTcF increase ≥60 ms during either treatment period (Table 6).

Table 6: Categorization of QTcF maximum increase from baseline by treatment group

	N (%) of Subjects by Maximum QTcF Increase from Baseline			
Study Day		<30 msec	30-<60 msec	≥60 msec
Treatment	N	n (%)	n (%)	n (%)
Day 1[a] through Day 10				
Placebo	35	27 (77.1%)	6 (17.1%)	2 (5.7%)
Asenapine 5 mg	38	31 (81.6%)	7 (18.4%)	0 (0.0%)
Asenapine 15 mg	38	28 (73.7%)	10 (26.3%)	0 (0.0%)
Quetiapine 375 mg	37	22 (59.5%)	14 (37.8%)	1 (2.7%)
Day 11 through Day 16				
Placebo	32	27 (84.4%)	3 (9.4%)	2 (6.3%)
Asenapine 10 mg	28	20 (71.4%)	8 (28.6%)	0 (0.0%)
Asenapine 20 mg	30	23 (76.7%)	7 (23.3%)	0 (0.0%)
Quetiapine 375 mg	29	20 (69.0%)	9 (31.0%)	0 (0.0%)

Source: 11.1.2.01.01.06
[a] Post dose

Sponsor's Table 38, page 95 of CSR for A750-1001

4.2.7.3 Safety Analysis

There were no deaths reported in this trial.

Three subjects experienced serious adverse events- a 51-year-old man, experienced severe atrial fibrillation on Day 1 after receiving a 5 mg dose of asenapine. He required hospitalization and was withdrawn from the trial. A 40-year-old woman, experienced a change in intensity of sinus tachycardia from mild to moderate on Study Day 9, and she was hospitalized. She was receiving quetiapine 375 mg b.i.d.. Study drug was discontinued and she was withdrawn from the trial. A 38-year-old woman experienced the adverse event of severe schizoaffective disorder 1 day after completing screening and starting to taper off her antipsychotic medication.

Nine subjects, including 2 who experienced serious cardiac adverse events, discontinued from the trial due to adverse events. One of these subjects discontinued from the trial due

to laboratory abnormalities (elevated LFT). Five discontinued due to psychiatric adverse events .

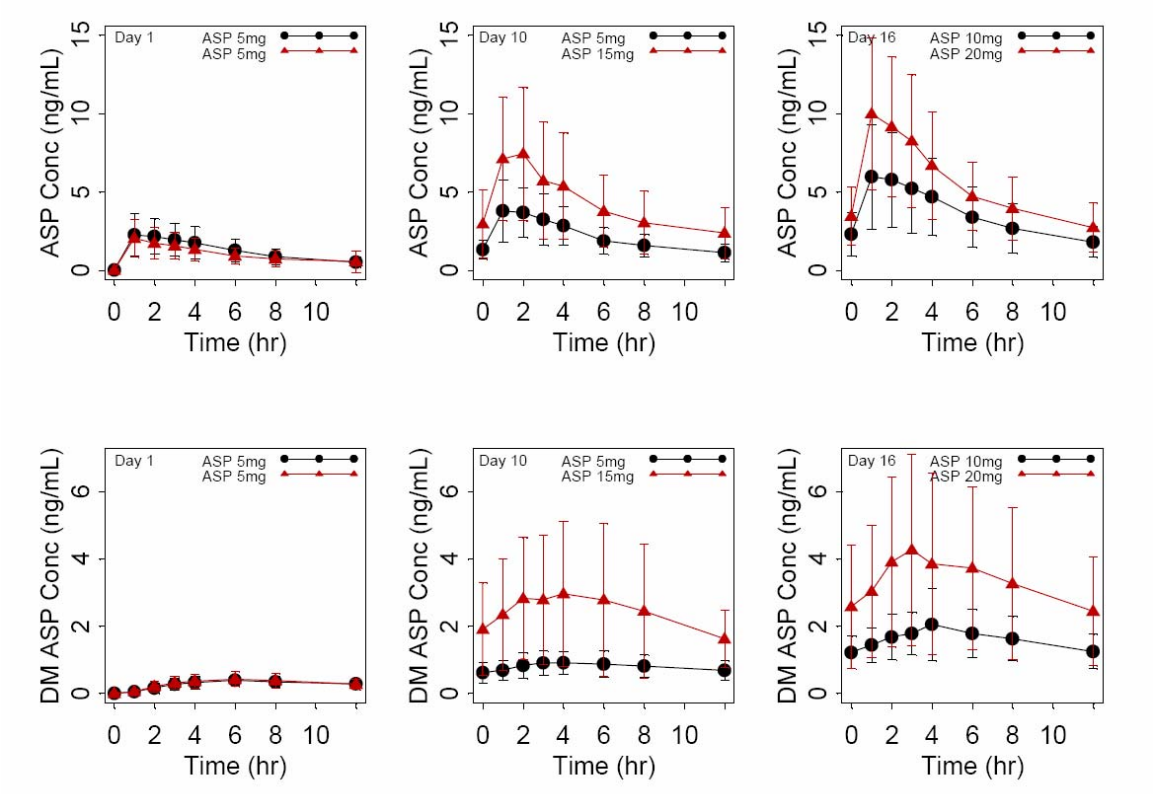
The adverse events, other than oral adverse events (dry mouth, dysgeusia), experienced by 3 or more asenapine-treated subjects and reported for a higher percentage of asenapine-treated subjects than quetiapine- or placebo- treated subjects were somnolence, restlessness, anxiety and dizziness, constipation and fatigue, akathisia, gait disturbance, nasal congestion, loose stools, and dysarthria.

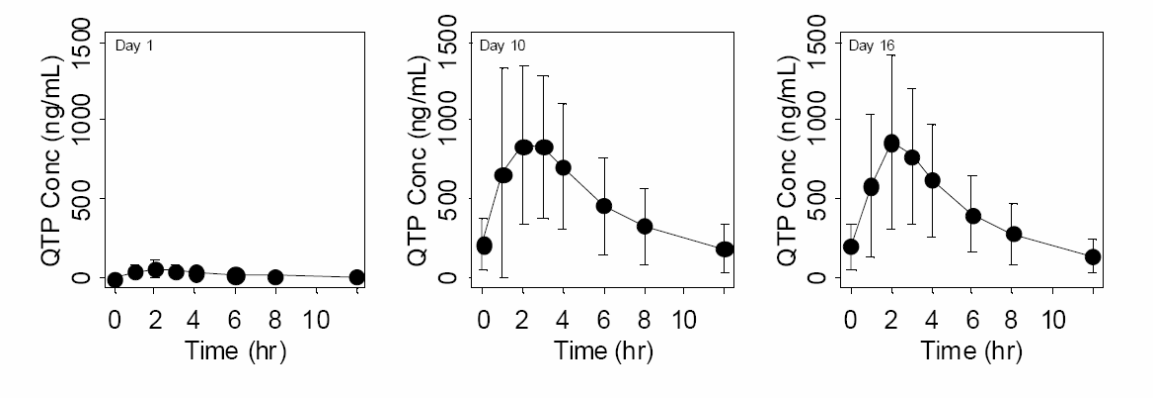
4.2.7.4 Clinical Pharmacology

4.2.7.4.1 Pharmacokinetic Analysis

Mean C_{max} and AUC values were similar between treatment groups on Day 1, when the initial dose was 5 mg for both groups. Differences between groups in mean C_{max} and AUC on Day 10 (5 or 15 mg b.i.d.) and Day 16 (10 or 20 mg b.i.d.) appeared less than proportional to dose for asenapine and asenapine N-oxide, but were proportional to dose for desmethyl asenapine. Mean t½ values on Day 16 were similar between groups for both asenapine and desmethyl asenapine.

Figure 2: Mean (±SD) Plasma Concentration-Time Profiles for Asenapine (ASP), des-Methyl Asenapine (DM ASP) and Quetiapine (QTP)





Sponsor's Figures 5 and 6, pages 106 and 109 of CSR for A750-1001

Table 7: Mean (%CV) PK estimates for Asenapine, des-Methyl Asenapine and N-Oxide Asenapine

Asenapine

Treatment Group = Asenapine 5/10 mg						
	Day = 1, Dose = 5		Day = 10, Dose = 5		Day = 16, Dose = 10	
	N = 35		N = 28		N = 25	
Parameter	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Cmax, ng/mL	35	2.61 (50.2)	28	4.23 (45.3)	25	6.56 (50.9)
tmax, hr	34	1.92 (51.5)	28	1.79 (46.9)	25	2.01 (46.0)
$AUC_{(0\text{-}tlqc)}$, ng*hr/mL	35	15.4 (49.1)		NA		NA
$AUC_{(0\text{-}T)}$, ng*hr/mL		NA	28	26.6 (38.4)	25	43.4 (53.1)
t½, hr		NA		NA	20	24.1 (41.3)
Treatment Group = Asenapine 15/20 mg						
	Day = 1, Dose = 5		Day = 10, Dose = 15		Day = 16, Dose = 20	
	N = 35		N = 33		N = 29	
Parameter	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Cmax, ng/mL	35	2.29 (55.1)	33	8.05 (54.2)	29	10.6 (48.2)
tmax, hr	34	2.48 (109)	33	1.66 (65.8)	29	1.70 (56.1)
$AUC_{(0\text{-}tlqc)}$, ng*hr/mL	35	12.4 (54.7)		NA		NA
$AUC_{(0\text{-}T)}$, ng*hr/mL		NA	33	51.2 (56.0)	29	66.1 (46.4)
t½, hr		NA		NA	20	22.4 (23.4)

Source: Appendix B.1 tables 1.2.1 through 1.2.6
N = Number of subjects included in the pharmacokinetic analysis
n = Number of subjects for this parameter
NA = Not applicable

Des-methyl asenapine

Treatment Group = Asenapine 5/10 mg

	Day = 1, Dose = 5 N = 35		Day = 10, Dose = 5 N = 28		Day = 16, Dose = 10 N = 25	
Parameter	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Cmax, ng/mL	35	0.410 (37.3)	28	1.02 (38.8)	25	2.21 (48.3)
tmax, hr	34	6.57 (30.9)	28	4.47 (40.1)	25	4.73 (46.7)
$AUC_{(0\text{-}tlqc)}$, ng*hr/mL	35	3.29 (44.9)		NA		NA
$AUC_{(0\text{-}T)}$, ng*hr/mL		NA	28	9.65 (38.9)	25	19.6 (35.7)
t½, hr		NA		NA	24	16.6 (31.8)

Treatment Group = Asenapine 15/20 mg

	Day = 1, Dose = 5 N = 35		Day = 10, Dose = 15 N = 33		Day = 16, Dose = 20 N = 29	
Parameter	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Cmax, ng/mL	35	0.457 (52.2)	33	3.21 (70.5)	29	4.52 (63.2)
tmax, hr	33	6.07 (30.2)	32	3.15 (42.7)	29	3.80 (42.1)
$AUC_{(0\text{-}tlqc)}$, ng*hr/mL	35	3.63 (52.7)		NA		NA
$AUC_{(0\text{-}T)}$, ng*hr/mL		NA	33	29.6 (72.5)	29	40.5 (64.9)
t½, hr		NA		NA	27	17.6 (46.3)

Source: Appendix B.2 tables 2.2.1 through 2.2.6
N = Number of subjects included in the pharmacokinetic analysis
n = Number of subjects for this parameter
NA = Not applicable

N-oxide asenapine

Treatment Group = Asenapine 5/10 mg

	Day = 1, Dose = 5 N = 35		Day = 10, Dose = 5 N = 28		Day = 16, Dose = 10 N = 25	
Parameter	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Cmax, ng/mL	35	0.0426 (154)	28	0.103 (119)	25	0.180 (48.7)
n>0	11		18		22	

Treatment Group = Asenapine 15/20 mg

	Day = 1, Dose = 5 N = 35		Day = 10, Dose = 15 N = 33		Day = 16, Dose = 20 N = 29	
Parameter	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Cmax, ng/mL	35	0.0481 (136)	33	0.221 (93.0)	29	0.303 (68.0)
n>0	13		27		24	

Source: Appendix B.1 tables 3.2.1 through 3.2.2
N = Number of subjects included in the pharmacokinetic analysis
n = Number of subjects for this parameter
n>0 = Number of subjects with Cmax greater than zero

Quetiapine

Treatment Group = Quetiapine 375 mg

	Day = 1, Dose = 25		Day = 10, Dose = 375		Day = 16, Dose = 375	
	N = 34		N = 28		N = 25	
Parameter	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Cmax, ng/mL	34	79.7 (60.9)	28	1180 (49.9)	25	1070 (35.9)
tmax, hr	34	1.89 (45.7)	28	2.39 (41.1)	25	2.11 (45.2)
$AUC_{(0\text{-}tlqc)}$, ng*hr/mL	34	312 (54.9)		NA		NA
$AUC_{(0\text{-}\tau)}$, ng*hr/mL		NA	28	6220 (48.9)	25	5610 (47.5)
t½, hr		NA		NA	17	7.15 (17.5)

Source: Appendix B.1 tables 4.2.1 through 4.2.3
N = Number of subjects included in the pharmacokinetic analysis (all-zero profiles excluded)
n = Number of subjects for this parameter
NA = Not applicable

Sponsor's Figures 5 and 6, pages 102-105, of CSR for A750-1001

4.2.7.4.2 Exposure-Response Analysis

The exposure-response relationships of QTcF with asenapine, with its metabolites, des-methyl-asenapine and asenapine N-oxide, and with quetiapine were evaluated using linear mixed effects modeling. The relationship between QTcF and asenapine, des-methyl asenapine, asenapine N-oxide, and quetiapine was simultaneously modeled using a linear model with slope and intercept parameters. The mathematical representation of the final model after model reduction was:

$$INT_i = \theta_1(1+\theta_6 \cdot SEX) + \eta_{BSV1} + \eta_{IOV1} \qquad if\ Day = -1\ or\ 1$$

$$INT_i = \theta_1(1+\theta_6 \cdot SEX) + \theta_7 + \eta_{BSV1} + \eta_{IOV1} \qquad if\ Day = 10\ or\ 16$$

$$SLPasp_i = \theta_2 + \eta_{BSV2} + \eta_{IOV2}$$

$$SLPqtp_i = \theta_5 + \eta_{BSV5}$$

$$QTcF_{ij} = INT_i + SLPasp_i \times Casp_{ij} \times I(asp) + SLPqtp_i \times Cqtp_{ij} \times I(qtp) + \varepsilon_{ij}$$

$$, where \qquad I(asp) = \begin{Bmatrix} 1 & treatment = asp \\ 0 & otherwise \end{Bmatrix} and \qquad I(qtp) = \begin{Bmatrix} 1 & treatment = qtp \\ 0 & otherwise \end{Bmatrix}$$

In these equations, QTcFij was the j^{th} QTcF observation for the i^{th} individual, θ1 represented the population mean estimate of the intercept, θ2 through θ5 represented the population mean estimate of the slopes, θ7 corresponded to mean QTcF prolongation by placebo effect, ηBSV represented the inter-individual variance of the corresponding parameter and was assumed to be a normal, independent, and identically distributed random variable with zero mean and variance ω_{BSV}^2(~NIID(0, ω_{BSV}^2)). The inter-occasion variance of the corresponding parameter was represented by ηIOV and was assumed to be a normal, independent, identically distributed random variable with zero mean and variance ω_{IOV}^2(~NIID(0, ω_{IOV}^2)). C_{asp} and C_{qtp} corresponded to the observed concentration for each compound and ε_{ij} represented the jth residual error for the ith individual and was assumed to be a normal, independent, identically distributed random variable with zero mean and variance σ^2 (~NIID(0, σ^2)).

Asenapine was the best predictor of QTcF for the asenapine treatment groups compared to its two metabolites. Given asenapine and inter-occasion variability for intercept and the asenapine slope in the model, inclusion of metabolites into the model did not significantly improve the model's predictive performance. Parameter estimates from the final model are summarized in the following table.

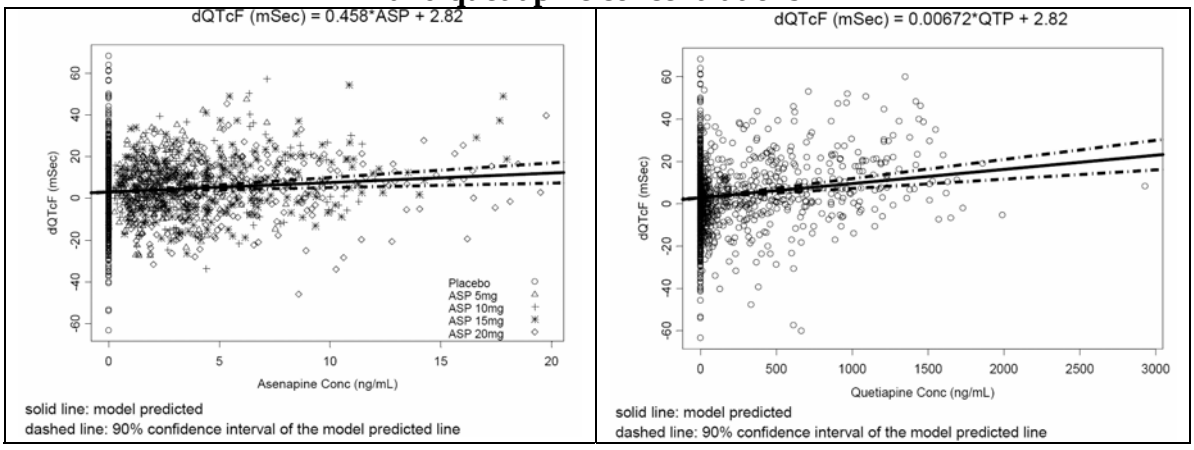
Table 8: Parameter estimates of the population exposure-QTc analysis

Parameter	Parameter Estimate	SE	CV%	90% CI (SE Derived)	90% CI (Bootstrap)
Intercept (ms)	399	2.78	0.697	(394,404)	(395.404)
BSV (ms)	15.3				
IOV (ms)	5.31				
Increase in Intercept by Placebo Effect (ms)	2.82	0.834	29.6	(1.44,4.2)	(1.35.4.14)
Gender Effect (%)	-4.31*	0.0075	-17.4	(-0.0555,-0.0307)	(-0.0552.-0.0302)
Slope for Asenapine (ms/[ng/mL])	0.458	0.147	32.1	(0.215,0.701)	(0.232.0.719)
BSV(ms/[ng/mL])	0.402				
IOV(ms/[ng/mL])	0.567				
Slope for Quetiapine (ms/(ng/mL))	0.00672	0.00141	21	(0.00439,0.00905)	(0.00423.0.00901)
BSV(ms/[ng/mL])	0.00374				
Residual Variability (ms)	9.58	0.344	3.59		

Sponsor's Table 52, page 13 of CSR for A750-1001

Plots of observed ΔQTcF vs. plasma concentrations for asenapine and quetiapine with model prediction are shown in Figure 3.

Figure 3: Plot of time-matched change from baseline in QTcF vs. plasma asenapine and quetiapine concentrations



Sponsor's Figure 7 and 8, pages 111-112 of CSR for A750-1001

The slopes for asenapine and quetiapine were estimated with reasonable precisions (CV 32% and 21% respectively) and their confidence intervals did not contain zero. The asenapine slope estimate indicates that there is a proportional and statistically significant relationship between QTcF and plasma asenapine concentrations, however the magnitude

of the slope is small and suggests an increase of 0.458 ms in QTcF per ng/mL asenapine concentration.

Table 9 reports expected QTcF increase with 90% confidence intervals at mean C_{max} of asenapine and quetiapine. The predicted estimates of mean QTcF prolongation at C_{max} for all doses of asenapine studied (5, 10, 15, and 20 mg b.i.d.) were less than 5 ms and less than those of quetiapine 375 mg b.i.d.. It is notable that the upper limit of the asenapine 90% confidence intervals for the maximum expected increase in QTcF (at C_{max}) for the 5 mg and 10 mg treatment groups was less than the expected maximum increase in QTcF (at C_{max}) for the quetiapine 375 mg treatment group.

Table 9: Expected QTcF Increase at Mean Cmax

Drug/Dose	Mean Cmax (ng/mL)	Expected QTcF Increase at Mean Cmax (ms)	90% CI (SE Derived)	90% CI (Bootstrap)
Asenapine 5mg	4.23	1.9	(0.9,3.0)	(1.0,3.0)
Asenapine 10 mg	6.56	3.0	(1.4,4.6)	(1.5,4.7)
Asenapine 15 mg	8.00	3.7	(1.7,5.6)	(1.9,5.8)
Asenapine 20 mg	10.7	4.9	(2.3,7.5)	(2.5,7.7)
Quetiapine 375 mg (Day 10)	1180	7.9	(5.2,11.0)	(5.0,11.0)
Quetiapine 375 mg (Day 16)	1070	7.2	(4.7,9.7)	(4.5,9.6)

Sponsor's Table 53, pages 113 of CSR for A750-1001

Reviewer's Comment: The reviewer was in general agreement with the sponsor's exposure-QTc modeling. See reviewer's analyses for exposure-ΔΔQTcF modeling, section 5.2.1. The assay sensitivity for this trial was in question in the absence of moxifloxacin arm. However, the effect of quetiapine on QT seemed similar to the data submitted with the paliperidone QT study (NDA 21999). See reviewer's analyses for further details on assay sensitivity.

Additionally, the sponsor also conducted exposure-response (report INT00036960) analyses to assess effect of asenapine administration on the QTc interval in patients with schizophrenia (Phase 3 ACTAMESA study).

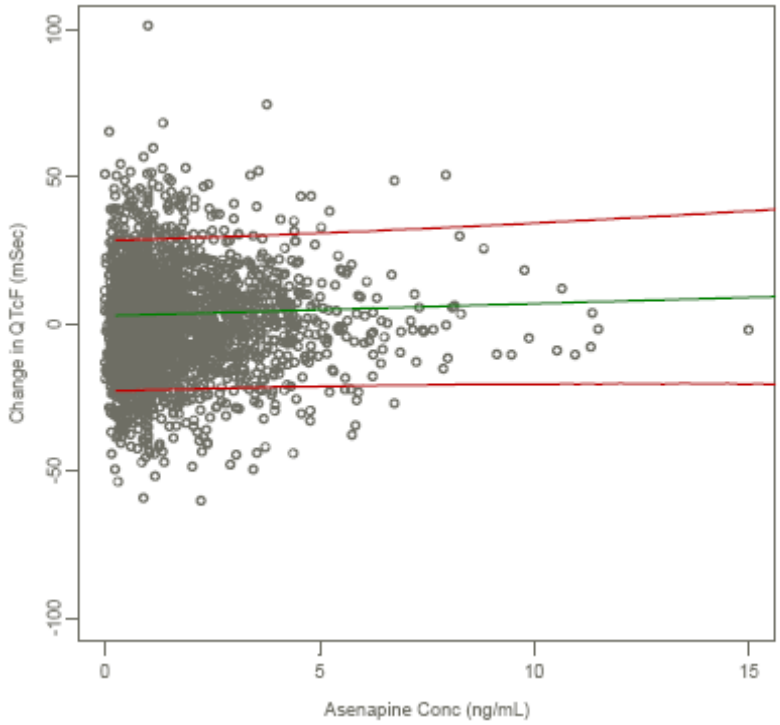
A total of 909 patients were included in the dataset for the asenapine group. All 909 patients included had at least one ECG measurement and 884 patients had at least 1 PK sample collected. Out of 884 patients, 853 patients had at least one PK sample above the quantification limit. Mean ± SD (range) average baseline QTcF (corrected QT according to Fridericia) and average baseline heart rate values were 405 ± 16.8 ms (362.7-470.3) and 74.9 ± 14.0 bpm (43-119), respectively. There were a total of 477 males and 432 females.

All data points prior to study drug administration were used for the assessment of the relationship between QTc and heart rate. Visually, QTcF is apparently dependent on heart rate. The population based correction (QTcP) appeared to correct the baseline QT interval for heart rate appropriately for this dataset, where the correction factor was estimated to be 0.4177. This factor is in between Bazett's (0.5) and Fridericia's (0.33). Nevertheless, all exposure-QTc analyses were performed using QTcF as the dependent

variable, because the thorough QTc exposure-response model was developed using QTcF and the main purpose of this analysis was to compare the Phase 3 exposure-response relationship to that of the thorough QTc trial.

When the Phase 3 ΔQTcF vs. concentrations data were compared to the unconditional prediction interval, they were visually well contained within the prediction intervals for all doses (Figure 4**)**. Overall the observed values show consistency with the prediction interval with a tendency of larger percentage below the median.

Figure 4: Unconditional Prediction Interval Overlaid with Observed ΔΔQTcF vs. Individual Predicted Asenapine Concentrations from Study 25517, A Phase 3 Study



Sponsor's Figure 4, page 20 from Study INT00036960

According to the sponsor, the exposure-QTcF relationship is consistent between the Phase 3 ACTAMESA study and the thorough QTc study (A7501001).

Reviewer's comment: The reviewer did not thoroughly evaluate the simulations conducted by the sponsor. The major evidence towards the effect on QT was available from the QT trial. The value and predictability of establishing such consistency was not immediately clear. However, it was reassuring to see the consistency between trials.

5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

The statistical reviewer's evaluation was based on the sponsor's data and in accordance with ICH E14 guidance on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.

This statistical reviewer also performed analysis based on the time-matched difference in QTcF of the drug and placebo after baseline adjustment at each time point (Table 10). The statistical reviewer used one-way ANOVA to calculate the 2-side 90% confidence interval of mean change in QTcF for each day at each time point.

Table 10:Reviewer's Analysis of Difference in Least Square Means from Placebo of Time Matched Change from Baseline in QTcF

Treatment Comparison	Time Post-Dose (hour)	N	Difference (SE)	90% Lower	90% Upper
Day 10					
Asenapine 5 mg b.i.d. vs Placebo	1	30	0.9 (4.2)	-6.0	7.9
	2	30	2.6 (3.4)	-3.0	8.2
	3	30	5.0 (3.9)	-1.5	**11.4**
	4	30	5.8 (3.0)	0.8	**10.8**
	6	30	4.1 (3.0)	-0.8	8.9
	8	29	5.8 (3.4)	0.3	**11.3**
	12	29	0.8 (3.6)	-5.1	6.6
Asenapine 15 mg b.i.d. vs Placebo	1	33	5.6 (3.7)	-0.6	**11.7**
	2	33	6.4 (3.4)	0.9	**12.0**
	3	33	8.7 (3.5)	3.0	**14.4**
	4	33	8.0 (3.4)	2.5	**13.6**
	6	33	5.1 (2.5)	0.9	9.2
	8	33	6.2 (3.2)	0.9	**11.3**
	12	32	1.2 (3.2)	-4.1	6.5
Day 16					
Asenapine 10 mg b.i.d. vs Placebo	1	27	3.4 (3.3)	-2.0	8.8
	2	27	10.5 (3.6)	4.5	**16.5**
	3	27	-0.4 (3.8)	-6.6	5.9
	4	27	9.3 (4.4)	2.0	**16.5**
	6	26	6.0 (3.8)	-0.3	**12.3**
	8	26	5.0 (4.3)	-2.0	**12.1**
	12	26	0.2 (4.9)	-7.8	8.3
Asenapine 20 mg b.i.d. vs Placebo	1	29	2.6 (3.5)	-3.2	8.4
	2	29	5.2 (3.6)	-0.7	**11.2**
	3	29	-1.1 (4.3)	-8.1	5.9
	4	28	4.9 (4.1)	-1.9	**11.6**
	6	29	-1.3 (3.8)	-7.5	4.9
	8	29	-1.8 (4.1)	-8.5	5.0
	12	29	-1.4 (4.6)	-9.0	6.2

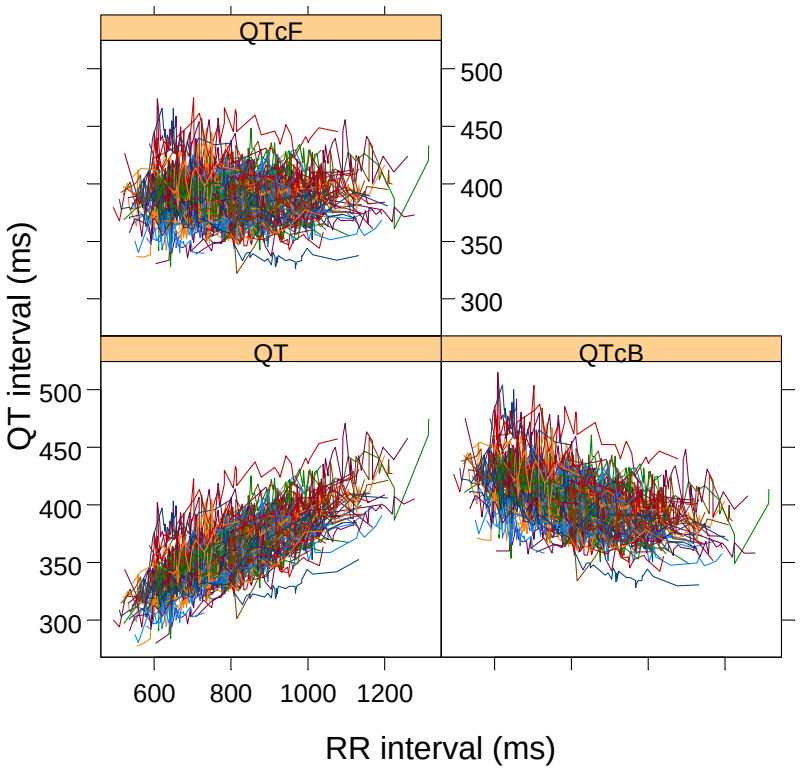
For all dose combinations of asenapine (5/10 mg b.i.d., 15/20 mg b.i.d.), the largest upper bounds of the two-sided 90% confidence interval for asenapine vs. placebo differences after baseline adjustments were above the 10 ms threshold.

Therefore, this statistical reviewer's analysis confirms the sponsor's results that asenapine at the study doses prolongs the QTc interval.

5.2 Clinical Pharmacology Assessments

The observed QT-RR interval relationship is presented in Figure 5 together with the Bazett's (QTcB), Fridericia (QTcF). The QTcF method was reasonable QT correction methods removing the heart rate effect in QT illustrated by a horizontal trend in the QTc vs. RR relationship. The QTcF correction method was used for the reviewer's concentration-QTc analysis.

Figure 5: Baseline day QT, QTcB, QTcF, and QTcLD vs. RR (Each Subject's Data Points are Connected with a Line).

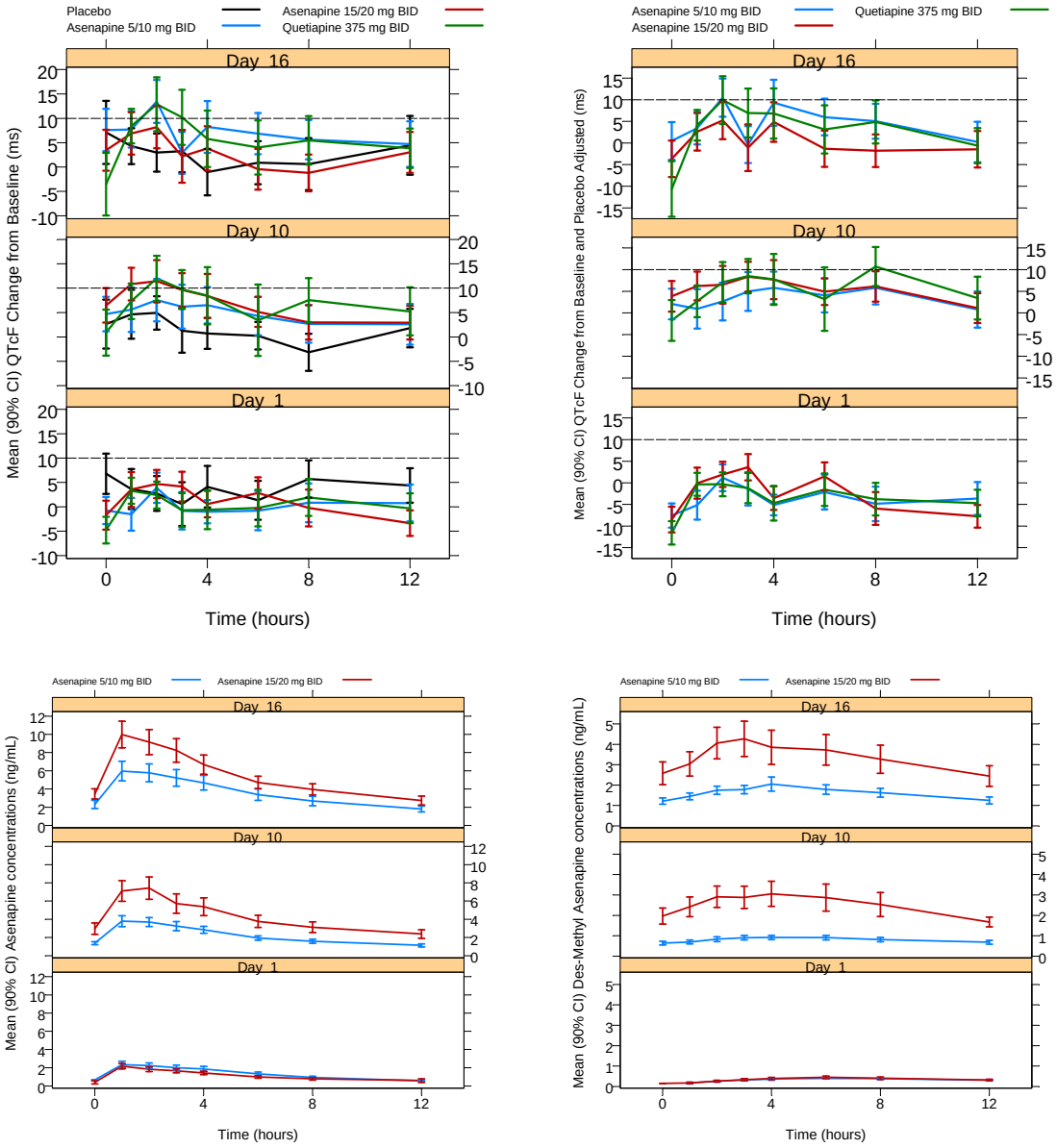


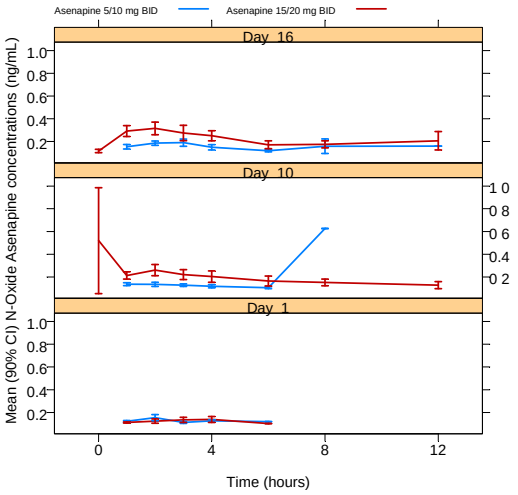
5.2.1 Exposure-Response Analyses

5.2.1.1 ΔΔQTcF and Concentration-Time Profiles

The mean ΔQTcF (change from baseline), ΔΔQTcF (change from baseline and placebo corrected), asenapine, des-methyl asenapine and n-oxide asenapine concentration profiles are shown in Figure 6.

Figure 6: Mean ΔQTcF (Change from Baseline), ΔΔQTcF (top right), and asenapine, des-methyl asenapine, n-oxide asenapine and quetiapine concentration profiles for all treatment groups on days 1, 10 and 16.





The maximum mean ΔΔQTcF of 8-10 ms occurs around 2-4 hours postdose for all treatment arms which closely matches with parent (asenapine or quetiapine) plasma concentration time profile. The graph (not shown) exploring delay in QT effect compared to parent drug concentration profile also supported use of parent drug concentration as a predictor (consistent with the sponsor's results).

5.2.1.2 Concentration-ΔΔQTcF Modeling for Asenapine

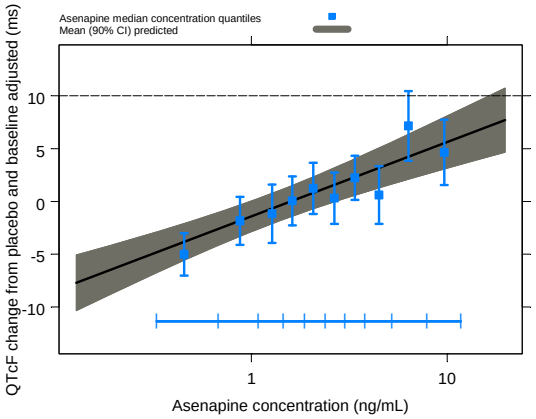
The relationship between asenapine concentrations and QT interval was investigated by using log-linear mixed-effects models. Data collected from the two asenapine dose groups at days 1, 10 and 16 were used for the asenapine concentration-QTcF analysis. Table 11 summarizes the results of the asenapine-QTcF analyses.

Table 11: Exposure-Response Analysis of asenapine associated ΔΔQTcF

ΔΔQTcF=Intercept+slope•log(asenapine concentration)		
Intercept, ms	-1.41 (-2.86; 0.04)	6.23
Slope, ms per log ng/mL	3.05 (2.08; 4.02)	3.27
Residual variability, ms	11.48	

The relationship between quetiapine concentrations and QT prolongation is visualized in Figure 7.

Figure 7: ΔΔQTcF vs. Asenapine Concentration with Observed Median-Quantile Concentrations and Associated Mean ΔΔQT (90% CI) overlaid (blue dots).



The expected QT prolongation at mean asenapine C_{max} (10.6 ng/mL) of suprtherapeutic dose (20mg b.i.d. dose) was 5.8 ms (8.3 ms, 90% upper confidence limit).

5.2.1.3 Concentration-ΔΔQTcF Modeling for Quetiapine

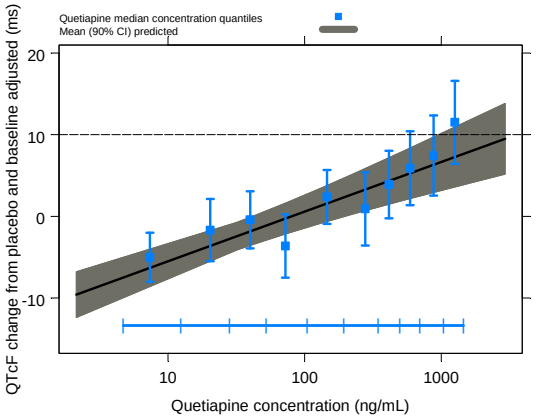
The relationship between quetiapine concentrations and QT interval was investigated by using log-linear mixed-effects models. Data collected from the 375mg b.i.d. quetiapine dose group at days 1, 10 and 16 were used for the quetiapine concentration-QTcF analysis. Table 12 summarizes the results of the quetiapine-QTcF analyses.

Table 12: Exposure-Response Analysis for Quetiapine

ΔΔQTcF=Intercept+slope•log(quetiapine concentration)		
Intercept, ms	-11.59 (-14.93; -8.24)	4.96
Slope, ms per log ng/mL	2.64 (1.78; 3.5)	1.98
Residual variability, ms	13.05	

The relationship between quetiapine concentrations and QT prolongation is visualized in Figure 8.

Figure 8: ΔΔQTcF vs. quetiapine concentration with observed median-quantile concentrations and associated mean QT (90% CI) prolongation overlaid (blue dots).



The expected QT prolongation at mean quetiapine C_{max} (1069.8 ng/mL) of quetiapine dose (375mg b.i.d. dose) was 7 ms (10 ms, 90% upper confidence limit).

5.2.1.4 Assay Sensitivity

Due to absence of moxifloxacin in the QT study, the assay sensitivity was established with the active control, quetiapine. This was performed by comparing the expsoure-response relationship from the current study with the quetiapine data submitted to NDA 21,999 (for paliperidone) as shown in Table 13.

Table 13. Comparison of the Exposure-Response Relationship for Quetiapine

	Study A750-1001 375 mg b.i.d. x 16 days Quetipine	NDA 21,999 Study R096477-SCH-1014 400 mg b.i.d. x 10 days Quetipine
Slope, ms per log ng/ml	2.6 (1.8; 3.5)	3.5 (2.6, 4.5)
Intercept, ms	-11.6 (-14.9; -8.2)	-15 (-21.2, -9.3)
Predicted ΔΔQTc, ms	6.7 ms (3.2, 10.2) for a mean C_{max} of 1000 ng/ml	9.1 ms (7.2, 11.1) for a mean Cmax of 1000 ng/ml

The exposure-response relationship for the two studies was found to be consistent. Therefore, in reviewer's opinion the data from the current study are interpretable.

6 CLINICAL ASSESSMENTS

None of the clinical events identified as of particular importance in the ICH E14 (death, serious ventricular arrhythmia, syncope and seizure) were observed in this study. Two patients had to be discontinued from the study due to atrial fibrillation and sinus tachycardia of moderate severity.

7 APPENDIX

7.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	**Schizophrenia**: The recommended dose range of Sycrest® is 5 mg to 10 mg given twice daily (BID). Sycrest® should be administered at an initial daily dose of 5 mg BID. An increase in dose to 10 mg BID is recommended only after clinical assessment. **Bipolar disorder**: The recommended dose of Sycrest® is 10 mg given twice daily (BID).	
Maximum tolerated dose	Asenapine 20 mg bid is the maximally tolerated dose in the population of subjects with schizophrenia; this dose has been studied in two trials: 041012 and A7501001 (the thorough QT/QTc trial).	
Principal adverse events	The principal adverse events considered associated with Sycrest®, based on the short-term placebo-controlled trials in schizophrenia and bipolar mania, were sedation, somnolence, akathisia, weight increase, and oral hypoesthesia. In the short-term placebo-controlled bipolar mania trials, dizziness generally occurred early in treatment and was of short duration. The incidence of akathisia was dose related. Long-term treatment with Sycrest® did not reveal any clinically relevant differences in the safety profile compared to the short-term trials. Somnolence, sedation and possible extrapyramidal symptoms are dose limiting adverse events.	
Maximum dose tested	Single Dose	5 mg (multiple trials)
	Multiple Dose	20 mg BID for 6 days (A7501001)
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) exposure parameters C_{max} 4.22 (51.2%) ng/mL $AUC_{0-\infty}$ 32.2 (40.1%) ng.h/mL Source: Module 2.7.2.3.2.1 and Module 2.7.2.3.2.5 – pooled analysis across 15 clinical pharmacology trials (N=334 and 331)
	Multiple Dose	Mean (%CV) exposure parameters C_{max} 10.6 (48.2%) ng/mL AUC_{0-12} 66.1 (46.4%) ng.h/mL Source: Module 2.7.2, Table 62, A7501001 (N=29)
Range of linear PK	Up to a dose of 5 mg BID, C_{max} and AUC for asenapine after sublingual administration increase proportional to the dose. Within the therapeutic dose range (5 – 10 mg BID) a deviation from dose-proportionality has been observed, with C_{max} and AUC increasing a factor 1.7 with a two-fold increase in dose. At supratherapeutic doses (> 10 mg BID), this deviation from dose-proportionality is more pronounced. Source: Module 2.7.2.3.2.8	

Accumulation at steady state	Accumulation ratios at 5 mg BID C_{max} – 0.95 AUC – 1.34 Source: Module 5.3.3.1 Clinical Trial Report 25542. Note that ratios are based on between subject comparisons. No within-subject accumulation ratios are available at the therapeutic dose.	
Metabolites	The following 5 metabolites have been detected in plasma in clinical studies: N-desmethylasenapine: Overall more than 10-fold reduction in binding affinity for human receptors examined compared to asenapine. asenapine N^+-glucuronide: No appreciable affinity for human receptors tested. N-desmethylasenapine-N-carbamoylglucuronide: Compound has not been profiled pharmacologically, but no activity is expected due to appreciable reduction (more than 10-fold) in binding affinity for the human receptors for the N-desmethyl metabolite, further loss of binding activity due to the fact that the nitrogen is no longer basic and expected inability to penetrate the brain. asenapine 11-O-sulfate: Receptor binding pattern broadly similar to asenapine, but compound does not penetrate the brain. asenapine N-oxide: 10 to 1000-fold reduction in binding affinity for human receptors compared to asenapine. Source: Module 2.6.2.2.4 and Module 2.4.2.1	
Absorption	Absolute/Relative Bioavailability	Absolute bioavailability (5 mg SL dose) Mean [95% CI]: 34.8 % [31.6 % - 38.7 %] Source: CTD 2.7.1.3.2 – No within-subject assessment of absolute BA has been done, therefore no estimate of between-subject variability in absolute BA is available.
	Tmax	Median (range) at 5 mg single dose • asenapine: 1.0 h (0.33 – 4.0 h) Source: Module 2.7.2.3.2.1, Table 50 – pooled analysis across 15 clinical pharmacology trials (N=334) • N-desmethylasenapine: 6 h (6 – 8 h) • asenapine N^+-glucuronide: 4 h (4 – 8 h) • asenapine 11-O-sulfate: 3.02 h (1.5 – 4.03 h) Source: Module 5.3.3.3 Clinical Trial Report 25546 (N=6, 6, 5) – Asenapine N-oxide concentrations were mostly below LLOQ, therefore no parameters were calculated. Plasma concentration-time profiles of N-desmethylasenapine-N-carbamoylglucuronide have not been assessed.

Distribution	Vd/F or Vd	Mean (%CV) Vd: 1731 L (10.3%) Source: Module 5.3.1.1 Report INT00035825, Table 2 – pooled analysis of IV data (0.5 mg asenapine infusion, N=5)
	% bound	Mean (SD) % protein bound: 95.9 (1.3) % Source: Module 5.3.3.3 Clinical Trial Report A7501017, Table 13 (N=33)
Elimination	Route	• Urine (49 %) • Feces (39 %) Source: Module 5.3.3.1 Clinical Trial Report 25532, Table 11 – Human ADME study (N=4)
	Terminal t½	Mean (%CV) at 5 mg single dose • asenapine 23.1 h (58.4 %) Source: Module 2.7.2.3.2.4, Table 53 – pooled analysis across 13 clinical pharmacology trials with PK sampling for at least 60 h (N=263) • N-desmethylasenapine 17.1 h (42.4 %) • asenapine N^+-glucuronide: 13.4 h (74.3 %) • asenapine 11-O-sulfate: 24.0 h (86.3 %) Source: Module 5.3.3.3 Clinical Trial Report 25546 (N=6, 6, 5) – Asenapine N-oxide concentrations were mostly below LLOQ, therefore no parameters were calculated. Plasma concentration-time profiles of N-desmethylasenapine-N-carbamoylglucuronide have not been assessed.
	CL/F or CL	Mean (%CV) CL: 51.9 L/h (10.3%) Source: Module 5.3.1.1 Report INT00035825, Table 2 – pooled analysis of IV data (N=5)

<table>
<tr><td rowspan="4">Intrinsic Factors</td><td>Age</td><td>Adults
In the age range tested (18 – 57 years) no effect of age on asenapine pharmacokinetics
Source: Module 5.3.3.5 Report INT00036661 - Population pharmacokinetic analysis of Phase 1/2 data
Elderly
The pharmacokinetics of asenapine have not been investigated in the elderly. However, a study (including pharmacokinetic sampling) is currently ongoing in elderly patients with psychosis (A7501021).
Pediatric/Adolescent
The steady-state pharmacokinetics in adolescent subjects (12 to 17 years) were compared with the pharmacokinetics in adult subjects in a clinical pharmacology study (A7501022). Up to and including the 5 mg BID dose level, asenapine pharmacokinetics in the adolescent population are similar to those observed in adults; however, in adolescents, the 10 mg BID dose did not result in higher exposure to asenapine compared to 5 mg BID.
Source: Module 2.7.2.3.3.3</td></tr>
<tr><td>Sex</td><td>No effect of gender on asenapine pharmacokinetics
Source: Module 5.3.3.5 Report INT00036661 - Population pharmacokinetic analysis of Phase 1/2 data</td></tr>
<tr><td>Race</td><td>No effect of race on asenapine pharmacokinetics, except for 13.8 % lower clearance in Black
Source: Module 5.3.3.5 Report INT00036661 - Population pharmacokinetic analysis of Phase 1/2 data</td></tr>
<tr><td>Hepatic & Renal Impairment</td><td>Hepatic impairment: substantial (5-fold) increase in exposure (AUC) only for severe hepatic impairment. For unbound asenapine a 7-fold increase in AUC was observed in this group.
mean % change versus normal
<table>
<tr><td></td><td>Mild</td><td>Moderate</td><td>Severe</td></tr>
<tr><td>C_{max}</td><td>-10 %</td><td>-43 %</td><td>+3 %#</td></tr>
<tr><td>AUC</td><td>+12 %</td><td>+12 %*</td><td>+453 %#</td></tr>
</table>
Source: Module 5.3.3.3 Clinical Trial Report A7501018, Table 7 (N=8, *N=7, #N=6)
Renal impairment: pharmacokinetics are similar for varying degrees of renal function
mean % change versus normal</td></tr>
</table>

<table>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td>Mild</td><td>Moderate</td><td>Severe</td></tr>
<tr><td>C_{max}</td><td>+34 %</td><td>-18 %</td><td>-29 %</td></tr>
<tr><td>AUC</td><td>+31 %*</td><td>+3 %#</td><td>+6 %#</td></tr>
<tr><td colspan="4">Source: Module 5.3.3.3 Clinical Trial Report A7501017, Table 8 (N=8, *N=7, #N=6)</td></tr>
</table>
</td></tr>
<tr><td>Extrinsic Factors</td><td>Drug interactions</td><td>
Effects of concomitantly administered drugs on asenapine pharmacokinetics – mean % change
- Paroxetine (20 mg QD – CYP2D6 inhibition)
C_{max} -13 % / AUC -9 %
Source: Module 5.3.3.4 Clinical Trial Report 25525
- Fluvoxamine (25 mg BID – CYP1A2 inhibition)
C_{max} +13 % / AUC +29 %
Source: Module 5.3.3.4 Clinical Trial Report 041033
- Imipramine (75 mg single dose – CYP1A2/2C19/3A4 inhibition)
C_{max} +17 % / AUC +10 %
Source: Module 5.3.3.4 Clinical Trial Report 25526
- Cimetidine (800 mg BID – CYP 3A4/2D6/1A2 inhibition)
C_{max} -13 % / AUC +1 %
Source: Module 5.3.3.4 Clinical Trial Report 25529
- Carbamazepine (400 mg BID – CYP3A4 induction)
C_{max} -16 % / AUC -16 %
Source: Module 5.3.3.4 Clinical Trial Report 25528
- Valproate (500 mg BID – UGT inhibition)
C_{max} +2 % / AUC -1 %
Source: Module 5.3.3.4 Clinical Trial Report 25527
</td></tr>
<tr><td></td><td>Food Effects</td><td>
Food (high-fat meal prior to or 4 h after administration): small decrease in exposure, probably due to increased liver blood flow
Mean change vs fasted
<table>
<tr><td></td><td>High-fat meal pre-dose</td><td>High-fat meal 4h post dose</td></tr>
<tr><td>C_{max}</td><td>-10 %</td><td>+2 %</td></tr>
<tr><td>AUC</td><td>-21 %</td><td>-13 %</td></tr>
<tr><td colspan="3">Source: Module 5.3.1.1 Clinical Trial Report 041029, Table 5 (N=26)</td></tr>
</table>
</td></tr>
</table>

Expected High Clinical Exposure Scenario	A theoretical worst case scenario would include severe hepatic impairment (7-fold increase in unbound AUC). However, as per ICH E14 guidance, such worst case scenario would be overruled by the limitations in the maximum dose level that can be administered based on safety or tolerability considerations. This dose level is 20 mg BID for asenapine. As a result, a formal calculation of the worst case exposure is considered redundant. In the thorough QT/QTc trial (A7501001) for asenapine the 20 mg BID dose regimen was included. Exposures achieved at 20 mg BID (the maximum dose tested) are included on the first page of this document.

7.2 TABLE OF STUDY ASSESSMENTS

Table 3 Schedule of procedures: screening phase

Test/Study Day	Screening[a]	-11	-10	-9	-8	-7	-6
		Optional					
Informed Consent	X						
Demographics	X						
Medical and Psychiatric History	X						
Physical Exam	X						
Vital Signs	X						
Urine Drug Screen[c]	X						
Thyroid Panel	X						
Clinical Laboratories	X						
Electrocardiogram	X						
Medication Tapering[b,d]		◄	—	—	—	—	►

[a] If no medication tapering was required, Screening and Day –5 could be the same day.
[b] Shorter or longer medication tapering (up to Day -20) was acceptable.
[c] If positive for phencyclidine, cocaine, amphetamines, opiates, or barbiturates, could be repeated 1 week later
[d] Medication tapering was to be done under the supervision of a physician.

Table 4 Schedule of procedures: single-blind placebo run-in phase

Test/Study Day	-5	-4	-3	-2	-1
Clinical Laboratories	X[b]			X	
Urine Drug Screen	X				
Serum Pregnancy Test[c]	X[b]				
Electrocardiogram					X[d]
Vital Signs[e]				X	
Supine/Standing Blood Pressure[e]				X	
PANSS/CGI-S/ESRS-A/TSQM					X
Administer Single-Blind Study Medication BID	X[f]	X	X	X	X

[a] Excluded antipsychotic medication had to be discontinued for at least 5 complete days.
[b] Not required if Screening and Day -5 were the same day.
[c] Women of childbearing potential only. Was not required for women who are post-menopausal and amenorrheic for at least 2 years.
[d] Triplicate ECG measurements taken prior to and 1, 2, 3, 4, 6, 8, and 12 hours following the morning dose.
[e] Taken at 08:00
[f] Cardiographic telemetry monitoring will begin at 0.5 hours prior to a.m. dose and continue throughout the Treatment Phase of the trial.

Table 6 Table of trial procedures: treatment phase (Periods 1 and 2)

Test/Study Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Electrocardiogram (Single Timepoint)[a]			X				X					X				
Electrocardiogram (Multiple Timepoints)[b]	X									X						X
Pharmacokinetics[b]	X									X						X
Supine/Standing Blood Pressure[c]		X				X			X					X		
Vital Signs[d]				X				X				X	X		X	
Vital Signs[e]	X	X				X					X			X		
Clinical Laboratories				X					X						X	
Thyroid Panel																X
PANSS/ESRS-A/CGI-S/CGI-C/TSQM																X
Administer Study Medication BID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Triplicate ECG measurements at 2 hours following the morning dose.
[b] Triplicate ECG measurements and samples for PK taken prior to and 1, 2, 3, 4, 6, 8, and 12 hours following the morning dose. In addition, samples for PK are taken on Day 16 at 16, 24, 36, and 48 hours following the morning dose.
[c] 1 and 3 hours following the morning dose
[d] 2 hours following the morning dose
[e] Prior to morning dose and 2 and 4 hours after morning dose.
[f] Morning dose only administered on Day 16

Table 7 Schedule of trial procedures: restabilization phase

Test/Study Day	+1	+2	+3	Closeout[a]
Physical Exam				X
Vital Signs				X
Electrocardiogram (Single Timepoint)				X
Clinical Laboratories				X
Thyroid Panel				X
Pregnancy Test				X

[a] Closeout = Discharge. Subjects could be discharged earlier if, in the opinion of the investigator, the subject was stable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christine Garnett
2/29/2008 01:03:49 PM
BIOPHARMACEUTICS

Pravin Jadhav
2/29/2008 01:15:28 PM
BIOPHARMACEUTICS

Joanne Zhang
2/29/2008 02:19:01 PM
BIOMETRICS

Yunfan Deng
2/29/2008 02:34:37 PM
BIOMETRICS

Suchitra Balakrishnan
2/29/2008 02:41:53 PM
MEDICAL OFFICER

Norman Stockbridge
2/29/2008 05:38:59 PM
MEDICAL OFFICER